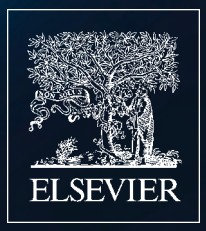
50
S1



VOLUME 50 SUPPLEMENT 1 February 2018
ISSN 1590-8658

Digestive and Liver Disease

An International Journal of Gastroenterology and Hepatology

Abstracts of the 51st Annual Meeting of the Italian Association for the Study of the Liver – A.I.S.F. Rome, February 22nd–23rd, 2018

Digestive and Liver Disease
Vol. 50/S1 (2018) 1–62
ELSEVIER

Digestive and Liver Disease

An International Journal of Gastroenterology and Hepatology

Vol. 50 Supplement 1 (2018)

Official Journal of:

Italian Association for the Study of the Liver (AISF)
Italian Association for the Study of the Pancreas (AISP)
Italian Association for Digestive Endoscopy (SIED)
Italian Society of Gastroenterology (SIGE)
Italian Society of Pediatric Gastroenterology and Hepatology (SIGENP)
Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)
Fédération Francophone de Cancérologie Digestive (FFCD)

Digestive and Liver Disease

Contents

Vol. 50 Supplement 1 (February 2018)

Index Medicus (MEDLINE), Current Contents/Clinical Practice,
Science Citation Index and EMBASE/Excerpta Medica
Sociedad Iberoamericana de Información Científica (SIIC)

Associato alla Unione Stampa Periodica Italiana

Abstracts of the 51st Annual Meeting of the Italian Association for the Study of the Liver – A.I.S.F. Rome, February 22nd–23rd, 2018

Digestive and Liver Disease 50(1S) (2018) 1–19

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Abstracts of the 51st A.I.S.F. – Italian Association for the Study of the Liver – Annual Meeting 2018 Rome, February 22nd–23rd, 2018: Selected oral communications

OC-01

Disease outcomes after DAA-induced SVR: Data from the resist-HCV cohort

V. Calvaruso[1], S. Petta[1], I. Cacciola[2], G. Cabibbo[1], F. Cartabellotta[3], A. Di Rosolini[4], A. Davì[4], M. Cannavò[5], M. Russello[5], M. Distefano[6], G. Scifo[6], F. Di Lorenzo[7], T. Prestileo[7], L. La Rocca[8], A. Montineri[8], G. Fiduli[9], A. Digiacomo[9], M. Cannizzaro[10], S. Madonia[10], A. Licata[11], G. Malizia[12], G. Alaimo[13], G. Bertino[14], B. Cacopardo[15], C. Iacobello[8], A. Averna[16], L. Guarneri[17], I. Scalisi[18], G. Mazzola[19], L. Mondello[20], V. Portelli[21], G. Squadrito[2], C. Cammà[1], G. Raimondo[2], A. Craxì[1], V. Di Marco[1], on behalf of RESIST-HCV

[1] *Unità Operativa Complessa di Gastroenterologia e Epatologia, Policlinico Paolo Giaccone, Università di Palermo, Italy*
[2] *UOC di Epatologia Clinica e Biomolecolare, Policlinico G. Martino, Università di Messina, Italy*
[3] *Unità Operativa Complessa di Medicina, Ospedale Buccheri La Ferla, Italy*
[4] *UO di Malattie Infettive dell'Ospedale Maggiore di Modica, Italy*
[5] *U.O Epatologia Ospedale Garibaldi-Nesima, Catania, Italy*
[6] *UO di Malattie Infettive, Ospedale Siracusa, Italy*
[7] *UO di Malattie Infettive, Ospedale Civico Di Cristina Benfratelli, Palermo, Italy*
[8] *UO di Malattie Infettive, Azienda Ospedaliero-Universitaria V. Emanuele-Ferrarotto-S.Bambino, Italy*
[9] *U.O.C. Medicina Interna Ospedale di Comiso, Italy*
[10] *U.O.C. di Medicina Interna, A. O. Villa Sofia-Cervello, Palermo, Italy*
[11] *U.O.C. di Medicina Interna, Policlinico Paolo Giaccone, Università di Palermo, Italy*
[12] *U.O.C. di Gastroenterologia, A. O. Villa Sofia-Cervello, Palermo, Italy*
[13] *U.O.C. Medicina Interna, Ospedale di Agrigento, Italy*
[14] *U.O.C. di Medicina Interna e d'Urgenza, A.O.U.P. Vittorio Emanuele, Catania, Italy*
[15] *U.S.C. di Malattie Infettive, ARNAS Garibaldi-Nesima, Catania, Italy*
[16] *U.O.C. Malattie Infettive Ospedale di Caltanissetta, Italy*
[17] *U.O.C. Malattie Infettive Ospedale di Enna, Italy*
[18] *UO di Medicina Interna, Ospedale di Mazara del Vallo, Italy*
[19] *UO di Malattie Infettive, Policlinico Paolo Giaccone, Università di Palermo, Italy*
[20] *UO di Malattie Infettive, Azienda Ospedaliera Papardo, Messina, Italy*
[21] *U.O.C. Malattie Infettive Ospedale di Trapani, Italy*

Background and aims: Large scale, real life data on the long term course of liver disease after HCV clearance obtained with DAAs are still scanty, and the separate effects on hepatic and non-hepatic causes of death still unclear.

Method: We evaluated 4147 patients (mean age: 65.7 ± 11.5 years, 57.6% males) included in the prospective RESIST-HCV cohort who started DAAs treatment in 22 centres between March 2015 and April 2017. All patients were follow after SVR to register liver-related and unrelated outcomes. The primary endpoint was the evaluation of survival since starting DAAs. Cox regression analysis was used to assess the predictors of liver-related and unrelated death.

Results: Patients were observed for a median of 50 weeks (range: 1–199), 934 (22.5%) had diagnosis of chronic hepatitis (F3 in >90%), 2851 (68.7%) had Child A cirrhosis and 362 (8.7%) had Child B cirrhosis. Overall, 3766 patients (90.8%) achieved SVR while 381 patients (9.2%) were HCV-RNA positive at the last control. Fifty-five patients (1.3%) died during the observation: 25 of them died for liver related causes and 30 for unrelated causes (16: cardiovascular disease, 6: sepsis, 8: other). The lack of SVR was associated with an increased incidence of overall mortality in comparison to patients with SVR (hazard ratio [HR]; 28.9; 95% confidence interval [CI]: 16.5–50.8; $p < 0.001$) and death from liver-related and unrelated causes (HR: 18.5, 95%CI: 8.2–41.3; $p < 0.001$ and HR: 45.5; 95%CI: 19.3–107.4; $p < 0.001$ respectively).

1590-8658/

By multivariate Cox regression analysis lack of SVR (HR: 14.9, 95%CI: 6.3–35.1; $p < 0.001$) and Child B cirrhosis (HR: 29.4, 95%CI: 3.8–223.9; $p < 0.001$) were independently related with liver mortality. Independent predictors of liver-unrelated mortality were no SVR (HR: 41.77, 95%CI: 17.30–100.87; $p < 0.001$), Child B cirrhosis (HR: 3.00, 95%CI: 1.36–6.22; $p = 0.006$), BMI (HR: 0.89, 95%CI: 0.81–0.98, $p = 0.023$) and diabetes (HR: 2.38, 95%CI: 1.13–5.00, $p = 0.022$).

Conclusion: In this real world setting using a variety of DAA regimens SVR reduced overall mortality and risk of liver-related and unrelated deaths at all stages of disease, nut mostly in Child A cirrhosis. The effect on cardiovascular deaths, which is evident also in the pre-cirrhotic stages deserves further follow up and investigation.

https://doi.org/10.1016/j.dld.2018.01.005

OC-02

Endoscopic radiofrequency ablation for the treatment of Gastric Antral Vascular Ectasia in cirrhotic patients: A bi-centric clinical and economical cost-effective analysis

M. Senzolo[1], S. Realdon[1], B. Simoncin[1], A. Zanetto[1], S. Caronna[2], G. Saracco[2], C. De Angelis[2], W. Debernardi-Venon[2]

[1] *Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Italy*
[2] *Gastroenterology and Hepatology Unit, Città della Salute e della Scienza, Turin, Italy*

Introduction: Gastric Antral Vascular Ectasia represents a significant cause of GI bleeding and transfusion dependent anaemia in cirrhotics. In 1/3 of cases it is refractory to argon plasma (APC) treatment and radiofrequency ablation (RFA) have been described to be potentially useful in heterogeneous cohorts of patients.

Aim: To prospectively evaluate the safety/efficacy of RFA for GAVE in cirrhotics with severe anaemia and to compare the cost and the advantage of the RFA.

Materials and methods: cirrhotics with GAVE, recurrent GI bleeding and/or severe chronic anaemia were enrolled at Padua and Turin Gastroenterology Units. RFA was performed by HALO90ULTRA Ablation System. All the clinical data (haemoglobin, number of transfusions, need of re-treatment), the GAVE endoscopic grade and the GI bleeding related hospitalizations were collected over a 6 months follow-up. An economic analysis was performed in the same interval time.

Results: 25 patients (mean age 70 years; 50% Child B) were enrolled. 21/25 did not respond to APC. RFA obtained eradication of GAVE in 100%. During the follow up, Hb increased from 8 ± 0.7 g/dL to 11 ± 1 g/dL ($p < .001$) and 15/25 patients were transfusion free. After RF, there was a reduction in the number of transfusions (25 ± 14 to 1 ± 1.7; $p < .001$) and a reduction in GI bleeding related hospitalizations (1.6 ± 0.4 to 0.3 ± 0.1; $p < .001$). The economic analysis showed a reduction of total cost (€ 13.933 to € 6.233), transfusions related cost (€ 10.048 vs. € 2448) and hospitalizations for GI bleeding related cost (€ 3407 vs. € 648), after RFA.

Conclusions: RFA is safe and effective procedure for cirrhotics with GAVE, mostly refractory to APC. Although the cost of RF is high, cost analysis shows a significant overall economic savings. RF could be considered as a first line treatment in severe form of GAVE.

https://doi.org/10.1016/j.dld.2018.01.006

OC-03

Epidemiology, predictors and outcomes of multi drug resistant (MDR) bacterial infections in patients with cirrhosis across the world. Final results of the "Global study"

S. Piano[1], V. Singh[2], P. Caraceni[3], R. Maiwall[4], C. Alessandria[5], J. Fernandez[6], E.C. Soares[7], D.J. Kim[8], S.E. Kim[9], M. Marino[10], J. Vorobioff[11], R. Ribeiro Barea[12], M. Merli[13], L. Elkrief[14], V. Vargas[15], A. Krag[16], S.P. Singh[17], L.A. Lesmana[18], C. Toledo[19], S. Marciano[20], X. Verhelst[21], F. Wong[22], N. Intagliata[23], L. Rabinowich[24], L.A. Colombato[25], S.G. Kim[26], A. Gerbes[27], F. Durand[28], J.P. Roblero[29], K.R. Bhamidimarri[30], T.D. Boyer[31], M. Maevskaya[32], E. Fassio[33], H.S. Kim[34], J.S. Hwang[35], A. Gadano[20], S.K. Sarin[4], P. Angeli[1], on behalf of the International Club of Ascites Global Study Group

[1] *Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine – DIMED, University of Padova, Padova, Italy*
[2] *Postgraduate Institute of Medical Education and Research, Chandigarh, India*
[3] *Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy*
[4] *Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India*
[5] *Division of Gastroenterology and Hepatology, AOU Città della Salute e della Scienza di Torino, University of Turin, Italy*
[6] *Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain*
[7] *Gastrocenter, University of Campinas, Campinas, Brazil*
[8] *Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Republic of Korea*
[9] *Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea*
[10] *Liver Unit, Hospital Dr. Carlos B. Udaondo, Buenos Aires, Argentina*
[11] *Universidad Nacional de Rosario, Rosario, Argentina*
[12] *Hepatologia, Hospital Regional de Mato Grosso do Sul (HRMS), Campo Grande, Brazil*
[13] *Gastroenterology, Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy*
[14] *Unit of Gastroenterology and Hepatology, University Hospital of Geneva, Geneva, Switzerland*
[15] *Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain*
[16] *Department of Medical Gastroenterology, Odense University Hospital, Odense, Denmark*
[17] *Department of Gastroenterology, Sriram Chandra Bhanj Medical College, Cuttack, India*
[18] *Digestive Disease & GI Oncology Center, Medistra Hospital, Jakarta, Indonesia*
[19] *Hospital Valdivia, Universidad Australe de Chile, Valdivia, Chile*
[20] *Liver Unit, Hospital Italiano, Buenos Aires, Argentina*

[21] *Department of Gastroenterology and Hepatology, Ghent University Hospital, Belgium*
[22] *Division of Gastroenterology, Department of Medicine, University of Toronto, Ontario, Canada*
[23] *Division of Gastroenterology and Hepatology, University of Virginia Health System, University of Virginia, Charlottesville, VA, USA*
[24] *Liver Unit, Department of Gastroenterology, Tel-Aviv Medical Center, Tel-Aviv, Israel*
[25] *Hospital Británico, Buenos Aires, Argentina*
[26] *Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea*
[27] *Liver Center Munich, Department of Medicine 2, University Hospital, LMU, Munich, Germany*
[28] *Hepatology & Liver Intensive Care, Hospital Beaujon, Clichy, France*
[29] *Universidad de Chile, Santiago, Chile*
[30] *Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA*
[31] *Department of Medicine, University of Arizona, Tucson, AZ, USA*
[32] *University of Moscow, Moscow, Russia*
[33] *Liver Unit, Department of Medicine, Hospital Alejandro Posadas, Buenos Aires, Argentina*
[34] *Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Republic of Korea*
[35] *Department of Internal Medicine, Keimyung University College of Medicine, Daegu, Republic of Korea*

Introduction: Bacterial infections are common and life-threatening in patients with cirrhosis. However, the epidemiology of bacterial infections across the world is poorly known.

Aims: In this multicenter intercontinental study, we looked for the epidemiology and the outcome of bacterial/fungal infections in hospitalized patients with cirrhosis across the world.

Methods: Hospitalized patients with cirrhosis and bacterial infection were prospectively included at 46 centers across the world. Demographic, clinical, microbiological and treatment data were collected at the diagnosis of infection and during the hospitalization. Patients were followed till death, transplantation or discharge. Bacteria resistant to at least one antibiotic in >2 classes were defined MDR.

Results: From October 2015 to September 2016, 1302 patients were included, 25% from North or South America, 32% from Asia and 43% from Europe. The most common infections were SBP (27%), UTI (22%) and pneumonia (19%). 740 patients had at least 1 positive culture and 959 microorganisms were isolated (58% Gram-neg; 38% Gram-pos; 4% Fungi). The global prevalence of MDR was 34% (95%CI = 31–37%). Independent risk factors for MDR infections were an infection in Asia (OR = 2.79; $p = 0.017$), particularly in India (OR = 7.94; $p < 0.001$) or in South America (OR = 2.23; $p = 0.053$), the use of antibiotics within 3 months before the hospitalization (OR = 1.92; $p = 0.001$), the category of infection (nosocomial [OR = 2.65; $p < 0.001$] and healthcare associated [1.62; $p = 0.032$]) and the site of infection (pneumonia [OR = 3.20; $p < 0.001$], UTI [OR = 2.48; $p < 0.001$] and skin and soft tissue infection [OR = 2.92; $p = 0.004$]).

MDR infections were associated with a lower rate of response to empirical antibiotic treatment (40 vs 68%; $p < 0.001$), a higher incidence of shock (27 vs 15%; $p < 0.001$) and new organ failures (42 vs 31%; $p = 0.001$), a lower rate of resolution of infection (82 vs 72%; $p = 0.003$), and a higher in-hospital mortality (31 vs 21%; $p = 0.004$) than those due to non-MDR bacteria.

Conclusions: The relevant differences in the etiology of bacterial/fungal infections across the world, particularly as regard to prevalence of MDR bacteria, highlight the need to develop different empirical antibiotic strategies across different continents and countries.

https://doi.org/10.1016/j.dld.2018.01.007

OC-04

Noninvasive prediction of esophageal varices by liver stiffness measurement and platelet values in patients with liver cirrhosis due to nonalcoholic fatty liver disease: A multicenter cross-sectional study

S. Petta[1], G. Sebastiani[2], E. Bugianesi[3], M. Viganò[4], V.W. Wong[5], A. Berzigotti[6], A.L. Fracanzani[7], Q. Anstee[8], F. Marra[9], M. Barbara[1], V. Calvaruso[1], C. Cammà[1], V. Di Marco[1], R. Lombardi[7], M.G. Rumi[4], A. Craxì[1], V. de Ledinghen[10]

[1] *Sezione di Gastroenterologia e Epatologia, Di.Bi.M.I.S, Università di Palermo, Italy*
[2] *Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal QC, Canada*
[3] *Division of Gastroenterology, Department of Medical Sciences, University of Torino, Torino, Italy*
[4] *Hepatology Unit, Ospedale San Giuseppe, University of Milan, Milan, Italy*
[5] *Affiliation of Vincent Wong: Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong*
[6] *Swiss Liver Center, Hepatology, University Clinic for Visceral Surgery and Medicine, Inselspital, University of Bern, Switzerland*
[7] *Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy*
[8] *Newcastle Upon Tyne Hospitals NHS Trust, Freeman Hospital, Newcastle upon Tyne, United Kingdom*
[9] *Dipartimento di Medicina Sperimentale e Clinica, University of Florence, Italy; Research Center DENOTHE, University of Florence, Italy*
[10] *Centre d'Investigation de la Fibrose Hépatique, Hôpital Haut-Lévêque, Bordeaux University Hospital, Pessac, France*

Introduction/aim: Baveno VI and extended Baveno VI criteria, based on the combination of liver stiffness (LS) with platelet (PLT) values, have been proposed to avoid unnecessary oesophagogastroduodenoscopy (OGD) screening for large oesophageal varices (OV) needing treatment (OVNT). We aimed to validate these criteria for OVNT in NAFLD cirrhosis.

Method: We evaluated 791 patients with NAFLD related compensated cirrhosis who had OGD within 6 month of reliable LSM. LSM was obtained by FibroScan machine by using M and/or XL probe. Baveno VI (LS < 20 and PLT > 150,000) and extended Baveno VI(LSM < 25 and PLT > 110,000) criteria were tested.

Results: Any grade OV were found in 31.2% of the population, while OVNT in 11.5%. Three-hundred thirty-eight patients had LSM by M probe only, 138 patients by XL probe only, and 314 by both M and XL probes. In the subgroup of 314 patients with both M and

XL probes (training set) Baveno VI and Baveno VI extended criteria spared 33.3% and 58% of OGD, respectively, missing 0.9% and 3.8% of large OV, respectively. In this subgroup we identified as the best thresholds for rule-out large OV, PLT > 110,000 and LSM < 30 kPa for M probe, and PLT > 110,000 and LSM < 25 kPa for XL probe. The use of these thresholds allowed sparing 68.5% and 65% of OGD, respectively, by missing 4.2% and 4.9% of large OV, respectively. These results were validated in the 338 patients with LSM by only M probe, and in the 138 with LSM by only XL probe. Sensitivity analysis considering separately all the centers overall confirmed the reported results.

Conclusion: The combination of PLT and LSM values – stratified according to FibroScan probe – could help to identify patients with compensated NAFLD-related cirrhosis at low risk of OVNT, in whom OGD screening can be safely sparred.

https://doi.org/10.1016/j.dld.2018.01.008

OC-05

Lack of reduction of serum alphafetoprotein during treatment with direct antiviral agents predicts hepatocellular carcinoma development in a large cohort of patients with HCV-related cirrhosis

C. Masetti [1], R. Lionetti [2], M. Lupo [3], M. Siciliano [4], V. Giannelli [5], F.R. Ponziani [6], E. Teti [7], C. Dell'Unto [8], S. Francioso [1], A. Brega [1], M. Montalbano [2], U. Visco-Comandini [2], C. Taibi [2], G. Galati [8], U. Vespasiani Gentilucci [8], A. Picardi [8], M. Andreoni [7], M. Pompili [6], A.M. Pellicelli [5], G. D'Offizi [2], A. Gasbarrini [4], A. De Santis [3], M. Angelico [1]

[1] *Liver and Transplant Unit, Tor Vergata University Hospital, Rome, Italy*
[2] *Infectious Diseases-Hepatology, National Institute for Infectious Diseases Spallanzani, Rome, Italy*
[3] *Department of Clinical Medicine, Gastroenterology Unit, Sapienza University of Rome, Rome, Italy*
[4] *Gastroenterology Unit, Catholic University of Rome, Rome, Italy*
[5] *Liver Disease Unit, Department of Liver Transplantation, San Camillo Forlanini Hospital, Rome, Italy*
[6] *Internal Medicine, Gastroenterology and Hepatology, A. Gemelli Hospital, Rome, Italy*
[7] *Department of Infectious Disease, Tor Vergata University Hospital, Rome, Italy*
[8] *Internal Medicine and Hepatology Unit, University Campus Bio-Medico, Rome, Italy*

Background and aims: Residual risk of HCC in HCV-infected cirrhotic patients treated with DAA is still debated. We investigated this issue in a large cohort of cirrhotic patients treated in 7 hospitals.

Methods: The cohort comprised 1045 cirrhotic patients who completed a treatment with DAA, with a median follow up of 17.3 months after the end of treatment (EOT), including 943 patients without a previous HCC and 102 treated for HCC before DAA. Patients were mostly males (59.9%), genotype 1b (44.6%), with Child-Pugh A cirrhosis (88.8%); mean age was 63 years.

Univariate and multivariate analysis were performed to detect significant predictors of HCC development. Kaplan–Meier curves were used to predict incidence of HCC in patients with and without reduction in AFP levels during treatment.

Results: SVR was achieved in 95.3% of patients. HCC developed in 95 (9.9%), including 54/943 (5.7%) *de-novo* and 41/102 (39%) recurrent tumors. *De-novo* tumors were more often unifocal ($p = 0.01$) and susceptible to curative treatments ($p = 0.029$). AFP levels decreased from 16.9 ± 36.2 mg/dl at baseline to 11.4 ± 55 mg/dl at EOT. At univariate analysis, predictors of HCC were older age, higher bilirubin and MELD score, prolonged INR, baseline and EOT AFP levels, previous HCC, virological failure and absent reduction of AFP during treatment. Kaplan–Meier curves showed a lower incidence of HCC in patients showing any reduction of AFP levels during treatment ($p = 0.006$). Those in whom AFP dropped to <6 ng/ml had the lowest risk ($p = 0.0001$). At Cox regression, MELD score (HR 1.14, c.l. 1.04–1.25, $p = 0.0002$), previous HCC (HR 6.57, c.l. 3.30–13.06, $p < 0.00001$) and lack of reduction of AFP (HR 3.02, c.l. 1.51–6.01, $p = 0.001$) were independent predictors of HCC.

Conclusions: Residual risk of HCC after DAA remains substantial. It is higher among patients with a previous HCC, high MELD score and without AFP reduction during treatment. Therefore, a strict surveillance for HCC is recommended, especially if AFP remains >6 ng/ml at EOT.

https://doi.org/10.1016/j.dld.2018.01.009

OC-06

Gender dimorphism in fibrosis dynamics in a murine model of chronic hepatic injury

M. Crescenzi [1], C. Frasson [2], M.F. Secchi [1], P. Burra [1], G. Basso [2], F.P. Russo [1]

[1] *Gastroenterology Section, Department of Surgery, Oncology and Gastroenterology, University Hospital Padova, Italy*
[2] *Department of Woman and Child Health, University of Padova, Institute of Pediatric Research Città della Speranza -IRP, Italy*

Background: A sexual dimorphism in liver inflammation and repair was previously demonstrated in a mouse model of acute liver injury.

Aims: To verify if gender-dependent mechanisms are responsible for liver fibrosis dynamics.

Method: A chronic hepatic injury was established in Balb/cJ mice by intra-peritoneal injection of CCl_4 and sacrificed at week 2, 6, 12 and after 8 weeks from the cessation of the treatment (recovery group). Fibrosis was evaluated by Sirius Red, collagen III and TIMP-1 were evaluated by Western blot, MMP-9 was analyzed by means of zymography in liver tissue.

Results: The amount of fibrosis in the recovery group was higher in females compared to males ($p = 0.032$). Collagen III was found lower in females than in males at week 2, with a significant increase along the treatment, but only in female mice. MMP-9 activity study revealed that at wk 2 female mice showed less activity compared to male mice ($p = 0.026$), with increasing of its activity from wk 2 to wk 6 ($p = 0.032$). Male mice showed a significant reduction ($p = 0.032$), and the difference in MMP-9 activity at wk 6 between female and male mice was statistically significant ($p = 0.032$). At wk 12 female mice showed less MMP-9 activity than male mice ($p = 0.026$). During the recovery period, male mice significantly reduced MMP-9 activity, differently from female mice ($p = 0.342$ and $p = 0.02$). TIMP-1 protein showed a progressive accumulation from week 2 to 12 only in females, with a significant decrease during the recovery period. No differences in TIMP-1 protein were found in male mice.

Conclusion: After a chronic liver damage, an imbalance in MMPs-TIMP-1 homeostasis was apparent in injured female livers. This could represent the key point to be explored in order to understand why females liver fails to properly regenerate, differently from male mice.

https://doi.org/10.1016/j.dld.2018.01.010

OC-07

Outbreak of Acute Hepatitis A involving young men in Lombardy region, Italy: Risk factors, clinical and virological characteristics

M. Iavarone[1], M. Viganò[2], C. Orcese[3], M. Coen[4], C. Oggioni[5], A. Spinetti[6], A. Soria[7], C. Galli[8], C. Tagliacarne[8], L. Scaramella[1], M. Merli[3], R. Rossotti[3], G. Gubertini[4], S. Merli[4], A. Piscitelli[5], A. Comelli[6], V. Castelli[7], D. Cereda[9], M. Gramegna[9], M. Puoti[3], A. Gori[7], M.G. Rumi[2], F. Castelli[6], P. Lampertico[1], L. Romanò[8]

[1] *"A. M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[2] *Division of Hepatology, Ospedale San Giuseppe, Università degli Studi di Milano, Milan, Italy*
[3] *Infectious Diseases Department ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[4] *First Division of Infectious Diseases ASST Fatebenefratelli – Sacco, Milan, Italy*
[5] *Quality and Clinical Risk Management Unit ASST Santi Paolo e Carlo, Milan, Italy*
[6] *University Department of Infections and Tropical Diseases University of Brescia and ASST Spedali Civili Brescia, Italy*
[7] *Clinic of Infectious Diseases, San Gerardo Hospital University of Milano-Bicocca, Monza, Italy*
[8] *Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy*
[9] *Direzione Generale Salute, Regione Lombardia, Milan, Italy*

Backgrounds and aim: Hepatitis A virus (HAV) is mainly transmitted via the faecal-oral route and/or contaminated aliments. In last decades, outbreaks of HAV in men who have sex with men (MSM) classified HAV as a sexually transmitted disease (STD). We aimed to analyse an HAV outbreak from 7 hospitals in Lombardy region in Italy with respect to patients' characteristics and viral phylogenetic analysis.

Methods: We prospectively analysed 244 cases of acute HAV between January and May 2017 recording for all patients' demographics data, risk factors, sexual orientation, co-morbidities and further STD infections. The phylogenetic correlation of the current circulating viruses among them and other HAV strains was assessed by sequencing of the VP1/2A region.

Results: Most patients were male (94%) with median age 33 (range 18–76) years. One hundred and thirty-three (55%) were MSM, 17% had a chronic liver disease, 19% were HIV positive, 5% were active drug users, 63% referred a possible sexual contact in last 3 months and 18% with a HAV positive partner. One hundred and eighty-one (74%) required hospitalization (median stay 7 days, range 2–44), no liver transplantation needed. The median ALT and bilirubin peak levels were 2368 (47–8914) UI/mL and 6.6 (0.4–18) mg/dL, respectively. Molecular phylogenetic analyses revealed that 93% patients were infected by HAV genotype IA and 7% by genotype IB. Moreover, all genotype IA cases belong to one of the three separate cluster recently reported in a multi-country European outbreak among MSM: 59% were infected with UK-strain (prevalence increasing during the last months of the outbreak), 40% with Netherlands-strain (prevalent at outbreak beginning) and 1% with Germany-strain.

Conclusion: Ongoing HAV in Lombardy primarily affects young MSM and is phylogenetically linked to current HAV outbreaks in European countries. Control measures, i.e. tailored vaccinations programs, must be taken to control further spreading.

https://doi.org/10.1016/j.dld.2018.01.011

OC-08

Specific human cholangiocarcinoma (CCA) subpopulations of cancer stem cells (CSCs) express DoubleCortin-Like Kinase 1 (DCLK1) and DCLK1 inhibition induces anti-cancer effects

L. Nevi[1], S. Di Matteo[1], G. Carpino[2], V. Cardinale[3], I. Zizzari[4], V. Ambrosino[1], D. Costantini[1], S. Safarikia[1], E. Manzi[5], A.M. Derose[6], F. Melandro[7], M.C. Bragazzi[3], G. Grazi[5], P.B. Berloco[7], F. Giuliante[6], E. Gaudio[8,9], D. Alvaro[1]

[1] *Department of Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy*
[2] *Department of Movement, Human and Health Sciences, Division of Health Sciences, University of Rome "Foro Italico", Rome, Italy*
[3] *Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy*
[4] *Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy, Rome, Italy*
[5] *Gastroenterology Unit, Regina Elena National Cancer Institute, Rome, Italy*
[6] *Surgery, Hepatobiliary Unit, Catholic University of the Sacred Heart School of Medicine, Rome, Italy*
[7] *Department of General Surgery and Organ Transplantation, Sapienza University of Rome, Rome, Italy*
[8] *Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Sapienza University of Rome, Rome, Italy*
[9] *Division of Human Anatomy, Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Sapienza University of Rome, Italy, Rome, Italy*

Cholangiocarcinoma (CCA) is an aggressive cancer with a low response to chemotherapeutics. Previously, we demonstrated that CCA is enriched of Cancer Stem Cells (CSCs); these features being associated with aggressiveness and drug resistance. In other solid tumours, DCLK1 has been demonstrated as a CSCs marker. The aim of this study was to evaluate *in vitro* the expression and the biological function of DCLK1 in mixed-intrahepatic-CCA (mixed-iCCA) and mucin-extrahepatic-CCA (mucin-eCCA). Surgical specimens of human CCA were enzymatically digested, immunosorted for specific CSC markers (LGR5, CD13, CD90, EpCAM, CD133) and, primary cell cultures were prepared. DCLK1 expression was analysed in primary CCA cell cultures by RT-qPCR, Western Blot (WB), immunofluorescence (IF) and ELISA. Functional studies were performed in immunosorted and unsorted cells by evaluating

the effects of LRRK2-IN-1, a selective DCLK1 inhibitor, on cell proliferation (MTS Assay, Population Doubling Time-PDT), apoptosis (Annessin-V-FITC/Propidium Iodide) and colony formation capacity (Clonogenic Assay). RT-qPCR and WB analyses demonstrated an increased expression of DCLK1 in mucin-LGR5$^+$-eCCA and mixed-CD133$^+$-iCCA cells compared to unsorted cells ($p < 0.01$). By IF, DCLK1 showed similar cytoplasmic localization in LGR5$^+$, CD133$^+$ cells and unsorted CCA cells. Very interestingly, DCLK1 was detected (ELISA) in the serum of CCA patients while it was almost undetectable in healthy controls. The DCLK1 inhibitor, LRRK2-IN-1 (5 μM) added for 3 days in CCA cell cultures, markedly impaired cell proliferation and increased PDT, induced apoptosis, decreased colony formation capacity and colony size in both iCCA and eCCA ($p < 0.01$ vs untreated control cells). The analyses of dose–response curves demonstrated how the anti-proliferative effect (MTS Assay) of LRRK2-IN-1 is dose-dependent (2.5–20 μM) with an IC50 of 9.61 μM in unsorted mucin-eCCA, 14.72 μM in unsorted mixed-iCCA, 4.51 μM in mucin-LGR5$^+$ and 9.61 μM in mixed-CD133$^+$ cells. In conclusion, DCLK1 expression characterizes specific CSC subpopulations of mixed-iCCA (CD133$^+$) and mucin-eCCA (LGR5$^+$) and its detection in CCA patients could represent a serum biomarker for CCA. Moreover, DCLK1 inhibition exerts anti-neoplastic effects in primary CCA cell cultures.

https://doi.org/10.1016/j.dld.2018.01.012

OC-09

Incidence, prevalence and mortality of Primary Sclerosing Cholangitis (PSC) in Italy: A population-based study

M. Carbone[1], A. Rocchetti[2], Y. Kodra[2], V. Manno[3], G. Minelli[3], F. Malinverno[1], A. Floreani[4], P. Invernizzi[1], S. Conti[3], D. Taruscio[2]

[1] *Division of Gastroenterology, Department of Medicine and Surgery, University of Milan Bicocca, Milan, Italy*
[2] *National Center for Rare Diseases, Istituto Superiore di Sanità, Rome, Italy*
[3] *Service of Statistics Istituto Superiore di Sanità, Rome, Italy*
[4] *Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy*

Introduction: Studies on PSC are mainly based on tertiary referral, retrospective case series with relevant selection bias, and population-based epidemiologic studies are scarce.

Aim: To estimate prevalence, incidence and mortality rates of PSC in Italy, using population-based data.

Methods: Two data sources were used: (i) the National Rare Diseases Registry (NRDR) run by the National Center for Rare Diseases of the Italian National Institute of Health (ISS); (ii) the National Mortality Database (NMD), run by the Service of Statistics of ISS, based on official data from the Italian National Institute of Statistics. In the period 2001–2014, all CSP cases (defined according to NRDR criteria) were selected. A deterministic linkage between NRDR and NMD was performed to evaluate the vital status and causes of death of the selected cases. Given that PSC does not have a specific code in ICD-10, the larger group "cholangitis" (code K83.0) was investigated.

Results: In the study period 502 PSC cases were identified (40% females), with an estimated diagnostic delay of 4 years. Since the NRDR reached full national coverage in 2011, PSC patients registered before where excluded; the mean number of new PSC patients registered in 2012–2014 was 61/year with a mean crude annual incidence of 0.10 per 100,000 persons. The estimated crude prevalence of PSC was 0.78 per 100.00. Mean age at disease onset and at diagnosis were 33 and 37 years, respectively. Ten-year survival was 92%; in 32% of deaths, the cause was "cholangitis".

Conclusions: This is the first description of epidemiology of PSC in Italy. For rare conditions such as PSC, population-based cohort studies are necessary, because incidence and prevalence rates of PSC are markedly lower and survival much longer than the ones reported from single-centre series. Moreover, the diagnostic delay highlights the need for increasing awareness on the disease.

https://doi.org/10.1016/j.dld.2018.01.013

OC-10

Dexamethasone reduces cholestasis-associated oxidative stress and inflammation in bile-duct ligated rats via CAR activation

D. Gabbia[1], L. Pozzo[2], G. Zigiotto[1], M. Roverso[3], D. Sacchi[4], A. Dalla Pozza[1], S. Bogialli[3], M. Guido[4], A. Floreani[5], S. De Martin[1]

[1] *Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy*
[2] *Institute of Agricultural Biology and Biotechnology, CNR, Pisa, Italy*
[3] *Department of Chemical Sciences, University of Padova, Padova, Italy*
[4] *Department of Medicine, General Pathology and Cytopathology Unit, University of Padova, Padova, Italy*
[5] *Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy*

Introduction: Glucorticoids (GCs) are successfully used in the treatment of cholestatic diseases, although their use remains controversial. Although the mechanism of dexamethasone (DEX) is the classical activation of GC receptor (GR), it has been suggested that other nuclear receptors (NRs), such as Pregnane X Receptor (PXR) and Constitutive Androstane Receptor (CAR) may be involved in its anti-inflammatory effect.

Aim: (1) To assess the therapeutic effect of a 2-week DEX treatment on hepatic damage in bile-duct ligated (BDL) rats; (2) to investigate DEX effect on hepatic NR and NF-kB activation, oxidative stress and BA composition.

Materials and methods: Cholestasis was induced by bile duct ligation (BDL) in 16 male Wistar rats; 8 sham-operated rats were used as controls. Eight cholestatic rats were treated by oral gavage with 0.125 mg/ml/kg die DEX for 14 days. Severity of cholestasis was assessed on histological examination and plasma biochemical parameters. Nuclear activation of NF-kB, GR, PXR and CAR was assessed by Western blot. CYP3A1 and CYP3A2 gene and protein expression were measured by qPCR and Western Blot, respectively. Oxidative stress was evaluated by measuring malondialdehyde (MDA), carbonylated proteins and GHS liver content. The bile acids CA, DCA, TCA, TCDCA, TDCA, GDCA, GCA were measured by LC–MS.

Results: As demonstrated by histology, DEX treatment counteracted cholestasis-related inflammation ($p < 0.01$ vs vehicle for p65 nuclear expression), and oxidative stress, since the cholestasis-induced significant alterations were restored by this drug. NF-kB activation was inversely correlated to CAR activation, which significantly increases after DEX treatment ($p < 0.01$ vs vehicle), without affecting CYP3A enzymes. Liver BA levels tended to decrease in

cholestatic rats, whereas they were similar to those of healthy rats in DEX-treated animals.

Conclusions: DEX counteracts inflammation and oxidative stress in BDL rats, probably *via* activation of CAR. This NR could represent a promising target for the management of inflammatory liver diseases.

https://doi.org/10.1016/j.dld.2018.01.014

OC-11

Reasons for recipient ineligibility for liver transplantation

M. Biolato[1], G. Marrone[1], C. Tarli[1], A. Liguori[1], L. Miele[2], G.L. Rapaccini[2], R. Calia[3], G. Addolorato[4], F. Pennestri[5], S. Agnes[3], A. Gasbarrini[4], A. Grieco[1]

[1] *Liver Transplant Medicine, Gastroenterological Area, Gastroenterological and Endocrino-Metabolical Sciences Department, Fondazione Policlinico Universitario Gemelli, Università Cattolica del Sacro Cuore, Roma, Italy*
[2] *Internal Medicine and Digestive DiseasesGastroenterological Area, Gastroenterological and Endocrino-Metabolical Sciences Department, Fondazione Policlinico Universitario Gemelli, Università Cattolica del Sacro Cuore, Roma, Italy*
[3] *Liver Transplantation and General Surgery, Abdominal Surgery Area, Gastroenterological and Endocrino-Metabolical, Sciences Department, Fondazione Policlinico Universitario Gemelli, Università Cattolica del Sacro Cuore, Roma, Italy*
[4] *Internal Medicine, Gastroenterology and Liver diseases, Gastroenterological Area, Gastroenterological and Endocrino-Metabolical, Sciences Department, Fondazione Policlinico Universitario Gemelli, Università Cattolica del Sacro Cuore, Roma, Italy*
[5] *Cardiology, Cardiovascular Area, Cardiovascular and Thoracic Sciences Department, Fondazione Policlinico Universitario Gemelli, Università Cattolica del Sacro Cuore, Roma, Italy*

Introduction and aim: Today, there are limited data on reasons of refusal of listing for liver transplantation candidates. Here we present frequency and reasons for decision of ineligibility for liver transplantation among referred adults in our center.

Patients and methods: Single center prospective study including adults with liver disease needing formal multidisciplinary assessment for liver transplantation.

Results: From 2015 to 2017, 316 patients were referred for liver transplantation in our center: 105 (33%) were transplanted, 24 (8%) are in the waitlist, 16 (5%) dropped for waitlist, 11 (3%) are under evaluation and 160 (51%) have been considered ineligible for waitlist.

Among 160 ineligible patients (76% male, mean age 55 years), 18 (11%) were referred for acute liver failure, 81 (51%) for chronic liver failure and 61 (38%) for Hepatocellular Carcinoma (HCC).

In 38 cases there was more than one motivation for ineligibility, so we recorded 192 ineligibility reasons in our cohort. Main ineligibility reason was presence of contraindications ($n = 90$, 47% of cases): psychiatric ($n = 19$, 10%), cardiological ($n = 17$, 9%) alcohol-related ($n = 10$, 5%), surgical (10, 5%), obesity ($n = 8$, 4%) respiratory ($n = 8$, 4%), infectious disease ($n = 8$, 4%), oncological ($n = 6$, 3%), malnutrition ($n = 4$, 2%). Secondary, ineligibility reasons were due to incorrect indications ($n = 69$, 36%): MELD < 15 after antiviral treatment or alcoholic abstinence ($n = 35$, 18%), conservative recovery after acute liver failure ($n = 18$, 9%), failure to downstage HCC ($n = 12$, 6%), HCC downstaged to T0 ($n = 4$, 2%). In 24 cases (12%) patient refused our program: transplantation refusal ($n = 15$, 8%), lost to follow-up ($n = 3$, 2%), choice other center ($n = 6$, 3%). 9 patients (5%) died because of complications before listing.

Conclusions: A final decision of ineligibility for liver transplantation occurred in half of our cohort and in one case out of three occur because of inappropriate or premature referral.

https://doi.org/10.1016/j.dld.2018.01.015

OC-12

Bridging therapies are not detrimental in patients with hepatocellular cancer waiting for liver transplant: A propensity score analysis

Q. Lai[1,2], U. Cillo[3], S. Iesari[1], A. Finkenstedt[4], M. Rossi[2], E. Tsochatzis[5], G. Otto[6], G.M. Ettorre[7], G. Tisone[8], M. Vivarelli[9], A.W. Avolio[10], M. Foguenne[1], J. Lerut[1], on behalf of the European Hepatocellular Cancer Liver Transplant Study Group

[1] *Starzl Unit of Abdominal Transplantation, St. Luc University Hospital, Université catholique Louvain, Brussels, Belgium*
[2] *Department of General Surgery and Organ Transplantation, Umberto I Hospital, Sapienza University, Rome, Italy*
[3] *Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy*
[4] *Department of Medicine I, Medical University Innsbruck, Innsbruck, Austria*
[5] *UCL Institute for Liver and Digestive Health and Royal Free Sheila Sherlock Liver Centre, Royal Free Hospital and UCL, London, UK*
[6] *Department of Transplantation and Hepatobiliary Surgery, University of Mainz, Mainz, Germany*
[7] *Division of General Surgery and Liver Transplantation, San Camillo Hospital, Rome, Italy*
[8] *Department of Transplant Surgery, Polyclinic Tor Vergata Foundation, Tor Vergata University, Rome, Italy*
[9] *Unit of Hepatobiliary Surgery and Transplantation, Azienda Ospedaliero-Universitaria "Ospedali Riuniti" Torrette Ancona, Italy*
[10] *Liver Unit, Department of Surgery, Agostino Gemelli Hospital, Catholic University, Rome, Italy*

Introduction: Patients with hepatocellular cancer (HCC) within Milan Criteria (MC) waiting for liver transplantation (LT) are approached in two different ways: direct LT vs. first treating the tumor using LRT. In these patients, the usefulness of LRT is still questioned.

Aim: To investigate the role of LRT in patients with MC-IN HCC waiting for LT in terms of risk of de-listing, intention-to-treat (ITT) survival and post-LT recurrence.

Material and Methods: the EurHeCaLT database allowed to identify 1177 MC-IN HCC patients listed for possible LT. Using propensity score matching, two homogeneous groups of directly transplanted ($n = 205$) vs. firstly LRT treated patients ($n = 205$) were studied.

Results: Median follow-up period was 3.6 years (IQR: 1.5–7.5). Comparing the groups, only two differences were observed, namely a longer median waiting time in the LRT-first group (5 vs. 4 months; $p = 0.04$) and a greater median dimension of the target lesion at the moment of LT or de-listing in the direct-LT group (2.0 vs. 1.7 cm; $p < 0.0001$). At multivariate Cox regression analysis, three independent risk factors for ITT-death were identified: MELD (HR = 1.04; $p = 0.005$), radiological progression beyond MC (HR = 2.04; $p = 0.03$) and alpha-fetoprotein slope >15 ng/mL/month (HR = 1.75; $p = 0.03$). At multivariate analysis, multimodal LRT approach (HR = 3.18; $p = 0.01$) and maximal diameter of the main HCC lesion (HR = 1.53; $p = 0.045$) were independent risk factors for post-LT recurrence. Repetitive LRT was not a significant risk factor in both the analyses. Survival over one year in de-listed patients was more common in LRT-first cases (5.9 vs. 1.0%; $p = 0.01$).

Conclusions: The use of (repetitive) LRT has no detrimental effect in MC-IN patients waiting for LT. LRT represents a tool allowing to further optimize the liver allocation process by selecting patients presenting a high-risk for drop-out (avoiding thereby futile liver transplants). The biological tumor response to the LRT is more than the LRT itself the strongest predictor of intention-to-treat survival and recurrence.

https://doi.org/10.1016/j.dld.2018.01.016

OC-13

Lymphoid infiltrate predicts prognosis of mass-forming intrahepatic cholangiocarcinoma undergoing complete liver resection

L. Vigano[1], C. Soldani[1], A. Lleo[2], L. Di Tommaso[3], B. Franceschini[1], M. Cimino[1], M. Donadon[1], G. Torzilli[1]

[1] *Department of Surgery – Division of Hepatobiliary & General Surgery, Humanitas Clinical and Research Center – IRCCS, Humanitas University – Rozzano, Italy*
[2] *Division of Internal Medicine and Hepatology, Department of Internal Medicine, Humanitas Clinical and Research Center, Humanitas University – Rozzano, Italy*
[3] *Pathology Unit, Humanitas Clinical and Research Center, Humanitas University – Rozzano, Italy*

Lymphoid infiltrate has shown a prognostic impact in numerous types of cancer, including hepatocellular carcinoma. No study focused on intrahepatic mass-forming cholangiocarcinoma (MFCCC). To assess the presence of lymphoid infiltrate and its prognostic impact in patients with MFCCC.

All consecutive patients undergoing surgery for MFCCC between 2005 and 2015 were considered. The inclusion criteria were complete resection (R0/R1) and follow-up ≥12 months. Patients with operative mortality were excluded. Tissue sections from MFCCC were immunostained for CD3+, CD4+, CD8+, Foxp3+ and CD68+. The number of positive cells was quantified using a computer-aided image analysis system. The percentage of positive cells in the analyzed area was computed.

Overall, 53 patients were analyzed. After a median follow-up of 41 months, 5-year OS was 56.1% and 3-year RFS was 40.1%. At univariate analysis, the following lymphoid infiltrate values had a prognostic impact: CD3+ >0.10% (OS $p < 0.001$, RFS $p < 0.001$); CD8+ >0.10% (OS $p = 0.044$, RFS $p = 0.001$), CD4+ >0.30% (OS = 0.094, RFS $p = 0.009$), and Foxp3+ present (OS $p = 0.097$). CD68+ cells were not associated with prognosis. At the multivariable analysis, CD3+ value was a prognostic factor of both OS and RFS [>0.10%, 5-year OS 66.9% vs. 18.2% if ≤0.10%, HR = 0.287, $p = 0.049$; 3-year RFS 48.1% vs. 9.1%, HR = 0.232, $p = 0.001$] and Foxp3+ was a negative prognostic factor of OS [present, 5-year OS 21.4% vs. 61.9% if absent, HR = 2.924, $p = 0.044$] (Figure 1). CD3+ values stratified prognosis in T1 patients (5-year OS 73.9%/14.3%, $p < 0.001$; 3-year RFS 60.8%/14.3%, $p < 0.001$), in N+ patients (OS 71.4%/0%, $p = 0.028$; RFS 42.9%/0%, $p = 0.011$) and in patients without lymph node metastases (RFS 49.7%/20.0%, $p = 0.062$).

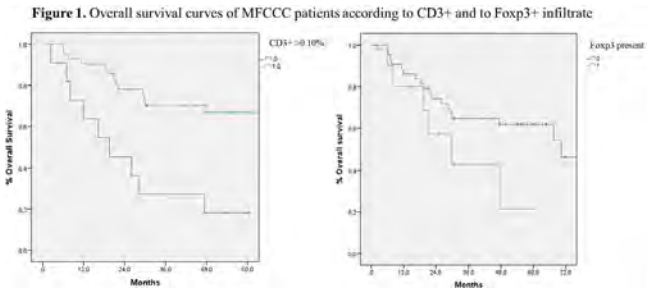


Figure 1.

The lymphoid infiltrate impacts prognosis of MFCCC after complete surgery. CD3+ infiltrate is associated with higher survival and lower recurrence risk, while Foxp3+ is associated with worse prognosis. CD3+ infiltrate allows to refine prognosis in early tumors and across different N stages.

https://doi.org/10.1016/j.dld.2018.01.017

OC-14

Fatty liver susceptibility to preservation injury using static cold storage versus dynamic machine perfusion

V. Siciliano[1], C. Berardo[1], L.G. Di Pasqua[1], V. Rizzo[2], B. Mannucci[3], P. Richelmi[1], A.C. Croce[4], A. Ferrigno[1], M. Vairetti[1]

[1] *Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy*
[2] *Department of Molecular Medicine, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy*
[3] *Centro Grandi Strumenti, University of Pavia, Pavia, Italy*
[4] *Institute of Molecular Genetics, Italian National Research Council (CNR), Pavia, Italy*

To overcome organ donor shortage, fatty livers could be used, although they appear susceptible to primary-non-function. To understand the mechanisms underlying preservation injury by static Cold-Storage (CS) or dynamic Machine-Perfusion (MP) in fatty livers, we investigated lipidomic profile effects in two rat models of NAFLD: methionine-choline-deficient (MCD) diet and obese Zucker (fa/fa) rats.

NAFLD was induced in Wistar rats by 2-week MCD diet; 12-week Zucker rats were also used. Livers were subjected to 6-hour preservation in UW solution at 4 °C (CS) or Krebs–Heinseleit solution at 20 °C (MP) and 2-hour reperfusion. Hepatic and biliary enzymes release, bile production and ATP/ADP ratio were evaluated. Liver fatty acid (FA) profiling was performed by Mass-Spectrometry (MS).

FA analysis showed that in Zucker and MCD rats the total saturated/polyunsaturated fatty acid (PUFA) ratio was 1.5 and 0.71, respectively. MCD rats showed a decrease in saturated stearic acid and polyunsaturated arachidonic acid and an increase in polyunsaturated linoleic acid. Higher AST and LDH release as well as biliary enzymes were found in Zucker versus MCD group after CS; lower

bile flow and comparable ATP/ADP ratio were observed in Zucker versus MCD group. No significant differences were detected comparing the MP in MCD versus Zucker rats as observed for hepatic and biliary enzymes release, bile flow and ATP/ADP ratio. Lower hepatic damage and increase bile flow were found in Zucker rat livers after MP as compared with CS.

Our results suggest that cellular injury is associated with the liver composition in FAs: Zucker livers with higher levels of saturated FA are more prone to CS injury respect to MCD livers with high PUFA content. The MCD livers appear less susceptible to CS. Thus, the lipidomic profile could be used to choose the appropriate preservation technique to exploit fatty livers for transplantation.

https://doi.org/10.1016/j.dld.2018.01.018

OC-15

Changes of indications for liver transplantation in the era of direct acting antiviral therapy in Europe

G. Perricone [1], R. Viganò [1], C. Mazzarelli [1], S. De Nicola [1], P.A. Cortesi [2], R. Facchetti [2], V. Karam [3], R. Adam [3], L.S. Belli [1]

[1] *Epatologia e Gastroenterologia, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[2] *Research Centre on Public Health (CESP), University of Milan-Bicocca, Monza, Italy*
[3] *Centre Hépatobiliaire, Assistance Publique-Hôpitaux de Paris, Université Paris-Sud, Hôpital Paul Brousse, F-94804 Villejuif, France*

Introduction: Direct-acting antiviral (DAA) therapy has changed the natural history of patients with decompensated cirrhosis (DC) secondary to hepatitis C virus (HCV).

Aim: We analyzed trends in liver transplant (LT) indications in Europe to explore potential impact of effective medical therapy on LT.

Materials and methods/results: This is a cohort study using the European Registry of Liver Transplantation (ELTR) database from 2007 to 2017. A total of 34,626 adult LT for HCV, hepatitis B virus (HBV), alcohol and nonalcoholic steatohepatitis (NASH) were identified. The cohort of LT patients was divided into interferon (IFN; 2007–2010), protease inhibitor (PI; 2011–2013), and second generation direct-acting antiviral (DAA; 2014–2016) eras. The percentage of LT for HCV varied significantly over time ($p < 0.0001$) decreasing from 38.9% in IFN era to 27.4% in the DAA era, while alcohol and NASH increased. Within the DAA era, the LT for HCV significantly decreased from 35.6% (2014) to 27.4% (2016). Three-year survival of DC-HCV recipients has improved from 65.3% in IFN era to 69.6% in PI era and to 77.9% in DAA era.

Conclusions: The availability of DAAs has reduced the percentage of HCV LT in Europe. Further reductions in LT are anticipated with increased access to DAA therapy. For the first time after many years survival of HCV recipients is improving since the advent of DAA.

https://doi.org/10.1016/j.dld.2018.01.019

OC-16

Pathological characteristics and early post-hepatic-resection outcome of patients with hepatocellular carcinoma occurred after hepatitis C treatment with new direct-acting antivirals: A multicenter cohort study

A. Vitale [1], F.P. Russo [1], C. Sposito [2], A. Cucchetti [3], G. Levi Sandri [4], S. Gruttadauria [5], S. Di Sandro [6], D. Ghinolfi [7], D. Nicolini [8], F. Trevisani [3], on behalf of the Special Interest Group on Hepatocellular Carcinoma, new anti-HCV therapies of the Italian Association for the Study of the Liver (AISF)

[1] *Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy*
[2] *General Surgery and Liver Transplantation Unit, University of Milan and Istituto Nazionale Tumori (National Cancer Institute), IRCCS*
[3] *Department of Medical and Surgical Science, Semeiotica Medica, University of Bologna, Bologna, Italy*
[4] *Division of General Surgery and Liver Transplantation, San Camillo Hospital, Rome, Italy*
[5] *Mediterranean Institute for Transplantation and Specialization Therapies (IRCCS-ISMETT), Palermo, Italy*
[6] *Division of General Surgery and Abdominal Transplantation, ASST Grande Ospedale Metropolitano Niguarda, 20162 Milan, Italy*
[7] *Hepatobiliary Surgery and Liver Transplantation, University of Pisa Medical School Hospital, Italy*
[8] *Hepato-biliary and Abdominal Transplantation Surgery, Polytechnic University of Marche, A.O.U. "Ospedali Riuniti", Ancona, Italy*

Introduction: There are no studies evaluating the pathological characteristics of recurrent or de novo hepatocellular carcinoma (HCC) occurring after anti-hepatitis-C (HCV) therapy with direct-acting antivirals (DAAs). Moreover, the early-postoperative-outcome of these HCC patients after hepatic resection is unknown.

Methods: Prospectively collected data from 420 consecutive patients with HCC and HCV cirrhosis undergoing liver resection in 18 Italian hepato-biliary surgical units between January 2014 and December 2016 were analyzed. Seventy-seven patients (18.3%) who develop recurrent or de novo HCC after DAAs therapy represented the study group, while the remaining 343 HCC patients formed the control group. The aim of this study was to compare these two groups in terms of pathological characteristics (primary endpoint) and early postoperative outcome (secondary endpoint). Inverse probability of treatment weighting (IPTW) was used to balance the preoperative characteristics of the two groups for the evaluation of the secondary endpoint.

Results: Primary endpoint (pathological characteristics): the study group showed significantly smaller tumors than the control group (25 mm vs. 35 mm), while no significant differences were found in terms of numbers of nodules, grading, vascular invasion, and satellitosis.

Secondary endpoint (early postoperative outcome): after IPTW, the 2 groups became well-balanced for most baseline characteristics including patient's age, performance status, comorbidities, tumor radiological features, alpha-fetoprotein level, severity of underlying liver disease, and extension of liver resection. Patients in the study group showed a significantly lower incidence of severe (Clavien score > 2) complications (3.4% vs. 9.3%) and early (within 6 months) postoperative mortality (2.0% vs 5.4%) than those in the

control group. SVR patients in the study group (71%) reached a 0% postoperative mortality.

Conclusion: DAAs therapy does not seem to modify the biological aggressiveness of recurrent or de novo HCCs undergoing liver resection. Conversely, DAAs therapy significantly improves the early postoperative outcome of these patients.

https://doi.org/10.1016/j.dld.2018.01.020

OC-17

Bacterial infections with and without acute-on-chronic liver failure in patients with cirrhosis and acute decompensation: Risk factors and outcome

M. Bartoletti[1,2], M. Baldassarre[1,3], M. Domenicali[1,3], R. Lewis[1,2], M. Giannella[1,2], M. Rinaldi[1,2], M. Tufoni[1], G. Zaccherini[1], M. Tamè[4], S. Berardi[5], L. Napoli[1], F.M. Pavarin[6], F. Angela[7], F. Trevisani[1], M. Bernardi[1], P. Viale[1,2], P. Caraceni[1,3]

[1] *Department of Medical and Surgical Sciences – Alma Mater Studiorum – University of Bologna, Bologna, Italy*
[2] *Infectious disease Unit – S. Orsola-Malpighi University Hospital, Bologna, Italy*
[3] *Center for Applied Biomedical Research (CRBA) – S. Orsola-Malpighi University Hospital, Bologna, Italy*
[4] *Gastroenterology Unit – S. Orsola-Malpighi University Hospital, Bologna, Italy*
[5] *End-stage Liver Disease Unit – S. Orsola-Malpighi University Hospital, Bologna, Italy*
[6] *Epidemiological Monitoring Center on Addiction, Mental Health DSM DP, Local Heath Unit Bologna, Italy*
[7] *Internal Medicine, Infermi Hospital of Rimini, A.U.S.L. of Romagna, Rimini, Italy*

Background and aims: Bacterial infections (BIs) are a frequent complication in patients with cirrhosis and often trigger the onset of acute-on-chronic liver failure (ACLF). This prospective observational study aims to describe the clinical and microbiological characteristics, risk factors and 1-year survival of patients admitted to hospital for acute decompensation (AD) with or without BIs and the relationship with the onset and outcome of ACLF.

Method: From January 2014 to March 2016 patients with cirrhosis admitted for AD at the S. Orsola-Malpighi University Hospital, Bologna, and at the "Infermi" Hospital, Rimini, were consecutively enrolled. Data were recorded at admission and during hospitalization. Survival was recorded up to 1-year. The diagnosis of BIs was confirmed by an Infectious Disease specialist.

Results: Among the 516 patients enrolled, 108 (21%) presented an infection at admission, while additional 61 (12%) developed a nosocomial infection. One-year survival was lower in patients with nosocomial (43%) and community acquired/healthcare related (52%) infections as compared to non-infected patients (65%) ($p < 0.001$). ACLF was diagnosed more frequently in infected than in non-infected patients (36 vs 26%; $p = 0.002$). At multivariate analysis higher MELD-Na score ($p = 0.001$), QuickSOFA score ≥ 2 points ($p = 0.004$), bacteremic ($p = 0.004$) and Multi Drug Resistant (MDR) infections ($p = 0.048$) were independent predictors of ACLF. One-year survival was similar in infected and non-infected patients without ACLF (71 vs 67%, $p = 0.337$). Contrariwise, BIs complicated by ACLF were associated to a significantly lower survival rate than ACLF precipitated by other events (23 vs 47%, $p = 0.010$). Finally, multivariate Cox regression showed that only BIs complicated by ACLF are associated to an increased risk of death ($p < 0.001$) independently from the severity of cirrhosis.

Conclusion: This large prospective study indicated that the adverse impact of BIs on long-term survival in decompensated cirrhosis is not universal, but limited to those patients who also develop ACLF. Both disease severity and microbiological factors predispose infected decompensated patients to ACLF.

https://doi.org/10.1016/j.dld.2018.01.021

OC-18

Forecasting liver disease burden

S. Robbins[1], L.A. Kondili[2], S. Blach[1], I. Gamkrelidze[1], A.L. Zignego[3], M.R. Brunetto[4], G. Raimondo[5], G. Taliani[6], A. Iannone[7], F.P. Russo[8], T. Santantonio[9], M. Zuin[10], L. Chessa[11], P.L. Blanc[12], M. Puoti[13], M. Vinci[14], E.M. Erne[15], M. Strazzabosco[16], M. Massari[17], P. Lampertico[18], M.G. Rumi[19], A. Federico[20], C. Ferrari[21], A. Ciancio[22], G. Borgia[23], P. Andreone[24], N. Caporaso[25], M. Persico[26], D. Ieluzzi[27], A. Gori[28], A. Gasbarrini[29], C. Coppola[30], S. Madonia[31], G.B. Gaeta[32], A. Andriulli[33], S. Montilla[34], H. Razavi[1], M. Melazzini[34], S. Vella[2], A. Craxi[35], on behalf of PITER Collaborating Group

[1] *Center for Disease Analysis, CDA Foundation | Polaris Observatory, Lafayette, CO, United States*
[2] *Center for Global Health, Istituto Superiore di Sanità, Rome, Italy*
[3] *Department of Experimental and Clinical Medicine, Interdepartmental Centre MASVE, University of Florence, Florence, Italy*
[4] *Department of Hepatology, University Hospital Pisa, Pisa, Italy*
[5] *Department of Internal Medicine, University Hospital of Messina, Messina, Italy*
[6] *Infectious and Tropical Diseases Unit, Umberto I Hospital – "Sapienza" University, Rome, Italy*
[7] *Department of Gastroenterology, University Hospital of Bari, Bari, Italy*
[8] *Department of Gastroenterology, University Hospital of Padua, Padua, Italy*
[9] *Department of Infectious Disease, Ospedali Riuniti, Foggia, Italy*
[10] *Liver and Gastrenterology Unit, ASST Santi Paolo e Carlo, Milan, Italy*
[11] *Liver Unit, University of Cagliari, Cagliari, Italy*
[12] *Department of Infectious Disease, S.M. Annunziata Hospital, Florence, Italy*
[13] *Department of Infectious Disease, Niguarda Cà Granda Hospital, Milan, Italy*
[14] *Hepatitis Center, Niguarda Cà Granda Hospital, Milan, Italy*
[15] *Department of Infectious Disease, University Hospital of Padua, Padua, Italy*
[16] *Department of Hepatology, San Gerardo Hospital, Monza, Italy*
[17] *Department of Infectious Disease, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy*
[18] *Department of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy*

[19] *Department of Gastroenterology and Hepatology, San Giuseppe Hospital, Milan, Italy*
[20] *Department of Hepatology and Gastroenterology, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy*
[21] *Department of Infectious Disease and Hepatology, University of Parma, Parma, Italy*
[22] *Gastoenterology Unit, Città della Salute e della Scienza-Ospedale Molinette Torino, Turin, Italy*
[23] *Department of Infectious Disease, Federico II University, Naples, Italy*
[24] *Department of Hepatology, University of Bologna, Bologna, Italy*
[25] *Gastroenterology Unit, Federico II University, Naples, Italy*
[26] *Department of Internal Medicine and Hepatology, Salerno University, Salerno, Italy*
[27] *Liver Unit, University Hospital Verona, Verona, Italy*
[28] *Department of Infectious Disease, San Gerardo Hospital, Monza, Italy*
[29] *Department of Internal Medicine and Gastroenterology, Catholic University of Rome, Rome, Italy*
[30] *Department of Hepatology, Gragnano Hospital, Naples, Italy*
[31] *Internal Medicine, Villa Sofia-Cervello Hospital, Italy*
[32] *Department of Infectious Disease, Second University of Naples, Naples, Italy*
[33] *Division of Gastroenterology Casa Sollievo Sofferenza Hospital, Istituto di Ricovero e Cura a Carattere Scientifico, San Giovanni Rotondo, Italy*
[34] *AIFA, Agenzia Italiana del Farmaco, Rome, Italy*
[35] *Gastroenterolgy and Liver Unit, DiBiMIS, University of Palermo, Palermo, Italy*

Introduction and aims: Advances in Hepatitis C virus (HCV) treatment have reinvigorated public health initiatives aimed at identifying affected individuals.

Method: Using data from the Italy PITER cohort and AIFA Registry, we modelled the impact on HCV disease burden according to different linkage to care scenarios.

Results: Under each scenario evaluated, HCV liver related mortality is expected to decline by 65%, achieving the WHO mortality target. Under the 40% linked-to-care-scenario, eligible patients to be treated will be depleted by 2025, resulting in a treatment rate decline moving forward. A targeted screening strategy in 2020–2025 in those individuals born in the years 1948–1978 could aliment the pool of patients to be treated by finding approximately 80% of F0–F3 cases. Under the PITER 60% linked-to-care-scenario, viremic infections will decline by 70% by 2030; but the patients eligible for treatment are expected to run out in 2028. If treatment is to be maintained at 33,700 through 2028, a screening strategy focusing on individuals born in the years 1958–1978 could capture 60% of infected patients. Under the PITER 80% linked-to-care-scenario, total viremic infections are forecasted to decline by 80% by 2030. The number of patients to be treated will run out by 2031; screening limited to those born in the years 1968–1978, which would capture 25% of infected cases, would be sufficient to sustain treatment at levels required to achieve the WHO targets.

Conclusion: Italy is meeting the WHO target of a 65% reduction in HCV liver related mortality by 2030. In the three PITER linkage-to-care-scenarios, the eligible pool of patients to be treated will run out between 2025–2031, leaving a significant proportion of individuals undiagnosed. In order to maintain or expand the number of treated patients per year to achieve the overall WHO goals, targeted screening strategies are required.

https://doi.org/10.1016/j.dld.2018.01.022

OC-19

Excellent 5-years survival for HBV cirrhotic patients developing a hepatocellular carcinoma during long-term analogs treatment

M. Iavarone[1], A. Loglio[1], G. Grossi[1], M. Viganò[2], F. Facchetti[1], M.G. Rumi[2], A. Sangiovanni[1], P. Lampertico[1]

[1] *CRC "A. M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy*
[2] *Division of Hepatology, Ospedale San Giuseppe, Università degli Studi di Milano, Milan, Italy*

Background and aims: Long-term oral nucleos(t)ide analog (NUC) therapy in patients with HBV chronic hepatitis or cirrhosis reduces the onset of hepatocellular carcinoma (HCC) but the clinical features of HCC and patients' survival in this specific population are still poorly characterized.

Material and methods: All HCCs developing between 2005 and 2016 in NUC-treated HBV patients were studied in our two Liver Centers. HCC surveillance and diagnosis were performed according to international guidelines. HCC occurring within first 6-months of NUC therapy were excluded. Endpoints of the study were clinical features of HCC and patients' outcome.

Results: 76 patients developed a HCC after 7 years (1–16) of NUC therapy: 67 (40–83) years-old, 84% male, 96% Caucasian, 95% HBeAg negative, 96% with undetectable HBV DNA, 89% genotype D, 80% with normal ALT levels, 87% cirrhotics (91% CPT A), median AFP levels were 4 ng/mL (1–3615), with 36% of the patients with AFP > 7 ng/mL. HCC was monofocal in 78%, with median diameter of 20 mm (range: 6–57), 92% BCLC 0 or A, 93% within Milan criteria, 3% with neoplastic portal vein thrombosis. As first-line treatment, 78% patients received radical therapies (39% RFA, 28% surgical resection, 11% liver transplantation – LT). Overall, a complete response was obtained in 61 (80%) patients: in 40 after a first-line treatment, in 3 after the second-line treatment, in 2 after a third-line treatment, while 16 underwent LT. During 45 (range 7–144) months of follow-up after HCC diagnosis, 19 (25%) patients died, 84% for HCC progression. The median time to recurrence of 20.2 (3–53) months and the overall 5-year survival was 69% (LT = alive) or 50% (LT = dead).

Conclusion: Most HCCs developing in NUC long-term treated patients are small, single tumors, within Milan criteria, BCLC 0/A and therefore amenable to curative therapies which led to excellent 5-year survival rates.

https://doi.org/10.1016/j.dld.2018.01.023

OC-20

Role of hepatitis B core-related antigen and antibodies to hepatitis B core antigen levels in the natural history of chronic HBV infection

G.P. Caviglia[1], A. Olivero[1], A. Ciancio[1], F. Tandoi[2], G. Troshina[1], C. Bosco[1], L. Boglione[1], M. Rizzetto[1], R. Romagnoli[2], G.M. Saracco[1], A. Smedile[1]

[1] *Department of Medical Sciences, University of Turin, Turin, Italy*
[2] *Department of Surgical Sciences, University of Turin, Turin, Italy*

Introduction: A reliable identification of chronic hepatitis B (CHB) patients requiring antiviral treatment could be challenging when chronic hepatitis (CH) is in a biochemical remission simulating a chronic infection (CI) profile.

Aim: To assess the added value of hepatitis B core-related antigen (HBcrAg) and anti-hepatitis B core antibody class IgG (anti-HBc IgG) levels for the discrimination between the different CHB phases.

Materials and methods: Serum samples of 132 CHB patients (13 CH-HBeAg+, 64 CH-HBeAg−, 21 low viremic CI-HBeAg− [fluctuating HBV DNA between 2000 and 20,000 IU/mL] and 34 true CI-HBeAg− [HBV DNA persistently <2000 IU/mL]) and 97 HBsAg−/anti-HBc+ subjects (51 occult HBV infection [OBI]+ and 46 OBI−) were analyzed. HBsAg, HBcrAg and anti-HBc IgG level were assessed by CLEIA (Lumipulse®, Fujirebio, Japan). Biomarkers levels were reported in LogIU/mL, LogU/mL and Log cut-off index (COI), respectively.

Results: Mean HBsAg, HBcrAg and anti-HBc IgG levels were different among CHB phases (one-way ANOVA, $p < 0.001$), with higher values in CH-HBeAg+ (4.47 ± 0.79 LogIU/mL, 6.9 ± 0.3 LogU/mL and 4.07 ± 0.69 LogCOI, respectively) and lower in true CI-HBeAg− (2.25 ± 1.26 LogIU/mL, 2.2 ± 0.4 LogU/mL and 3.29 ± 0.52 LogCOI, respectively). Area under the curve (AUC) for discriminating between low viremic and true CI-HBeAg− was 0.736 for HBsAg, 0.749 for HBcrAg and 0.648 for anti-HBc IgG; a higher accuracy (AUC = 0.812) was obtained combining HBcrAg and anti-HBc IgG. Among HBsAg−/anti-HBc+ subjects, anti-HBc IgG levels were different between OBI+ and OBI− (1.16 ± 0.60 vs. 0.78 ± 0.64 LogCOI, $p = 0.004$) with AUC = 0.671.

Conclusions: The combination of HBcrAg and anti-HBc IgG levels may improve the correct identification of true CI-HBeAg− patients (HBV DNA persistently <2000 IU/mL) not requiring antiviral therapy. Anti-HBc IgG is the only circulating HBV marker detectable and quantifiable in HBsAg− subjects with previous HBV exposure and may help clinicians to predict HBV reactivation in OBI+ subjects undergoing pharmacological immunosuppression.

https://doi.org/10.1016/j.dld.2018.01.024

OC-21

IFN-free DAA treatment of cirrhotic HCV patients with or without history of HCC: A multicenter prospective trial in Italy

A. Sangiovanni[1], E. Alimenti[1], M. Barone[14], L.S. Belli[13], E. Biganzoli[2], G. Borgia[3], M. Brunacci[4], M.R. Brunetto[5], R. D'Ambrosio[1], S. Fargion[6], R. Filomia[7], M. Gambato[8], R. Gattai[5], E.G. Giannini[4], S. Maimone[7], L. Marzi[12], F. Oliveri[5], G. Pellegatta[4], G. Raimondo[7], M. Rumi[9], F.P. Russo[8], I. Serio[10], N.M. Terreni[11], L. Valenti[6], E. Villa[12], P. Lampertico[1]

[1] *Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico – University of Milan, Milan, Italy*
[2] *Unit of Medical Statistics, Biometry and Bioinformatics, IRCCS Istituto Nazionale Tumori, Milan, Italy*
[3] *Department of Clinical Medicine and Surgery, Section of Infectious Diseases, University of Naples 'Federico II', Naples, Italy*
[4] *Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Genoa, Italy*
[5] *Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, University Hospital of Pisa, Pisa, Italy*
[6] *Internal Medicine and Metabolic Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy*
[7] *Division of Clinical and Molecular Hepatology, University Hospital of Messina, Messina, Italy*
[8] *Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology, Padua University Hospital, Padua, Italy*
[9] *Division of Hepatology, Ospedale San Giuseppe, Università degli Studi di Milano, Milan, Italy*
[10] *Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy*
[11] *Division of Gastroenterology, Valduce Hospital, Como, Italy*
[12] *Gastroenterology Unit, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy*
[13] *UOC Epatologia e Gastroenterologia, Ospedale Niguarda, Milan, Italy*
[14] *Gastroenterology Unit, Department of Emergency and Organ Transplantation (D.E.T.O.), University of Bari, Italy*

Aim: Aim of this study was to evaluate whether the incidence of de novo or recurrent HCC increases after starting direct antiviral agents (DAA) in cirrhotic patients.

Patients and methods: In a multicenter prospective cohort enrolled between June 2014 and September 2017, 1028 consecutive HCV cirrhotic patients with no history of HCC, and 120 consecutive patients with radiological complete response to HCC treatment were enrolled and treated with IFN-free DAA. SVR was obtained in 957 (97%) cirrhotic patients (Group 1): 559 (58%) males, median age 66 years (22–85), pending SVR in 36 cases and in 111 (96%) patients with HCC (Group 2): 75 (68%) males, median age 70 years (46–86)], pending SVR in 5 cases. Multivariable Cox regression analysis was performed to assess the association of variables with HCC development and recurrence.

Results: During 62 weeks follow up (range 1–174), 33 de novo HCC developed in Group 1, including 9 out of 94 with undefined/non-malignant nodules (yearly incidence 3.4%), and during a 49 weeks follow up (range 4–116) 31 HCC recurred in Group 2 (yearly incidence 29.7%). A peak of HCC instant incidence at 47 weeks in Group 1 and at 30 weeks in Group 2 were observed. By multivariable Cox regression models, presence of hepatic nodules (HR = 3.25 CI 1.5–7.0, $p = 0.003$, with a time dependent relation, and Child-Pugh (HR = 1.6, 95% CI 1.2–2.1, $p = 0.001$) were associated with de novo HCC incidence in group 1, while overall no variables showed evidence of association with HCC recurrence.

Conclusion: In SVR patients IFN-free DAA treatment of HCV cirrhotic patients allows a progressive decrease of de novo and recurrent HCC incidence after a non-significant increased number of HCC observed at 47 weeks after stating DAA in patients without history of HCC and at 30 weeks in patients with history of HCC.

https://doi.org/10.1016/j.dld.2018.01.025

OC-22

Combination of HBV serological markers can predict the burden and productivity of intrahepatic HBV reservoir and disease progression in HBeAg-negative chronic hepatitis B infection

R. Salpini[1], L. Colagrossi[1], U.S. Gill[2], A. Battisti[1], L. Piermatteo[1], N. Hansi[2], C.F. Perno[3], P.T.F. Kennedy[2], V. Svicher[1]

[1] *University of Rome Tor Vergata, Department of Experimental Medicine and Surgery, Rome, Italy*
[2] *Hepatology, Centre for Immunobiology, Blizard Institute, Barts and The London SMD, QMUL, London, United Kingdom*
[3] *University of Milan, Milan, Italy*

Introduction and aim: Limited data exist on intrahepatic compartment and how serum HBV markers (HBV-DNA, HBsAg, HBcrAg) reflect intrahepatic HBV reservoir (total HBV-DNA [itHBV-DNA] and cccDNA) and its transcriptional activity (pgRNA). Better virological characterisation is required to inform treatment decisions particularly in those with HBV DNA <20,000 IU/ml.

Materials and methods: Liver tissue from 84 eAg-negative chronic hepatitis B patients (pts) was studied. cccDNA, itHBV-DNA and pgRNA were assessed by qPCR. Serum HBcrAg and HBsAg were measured by Lumipulse (Fujirebio) and COBAS HBsAgII (Roche Diagnostics) assays. Correlations between peripheral and intrahepatic compartments were defined by Spearman test. AUROC was used to define thresholds of peripheral parameters to predict intrahepatic reservoir (cccDNA < 1logcps/1000 cells) and fibrosis stage (determined by Ishak score).

Results: Pts across the groups were age and sex matched: median age 35 years (range 28–42), male: 69%. Overall, serum HBV-DNA and HBcrAg positively correlate with cccDNA (Rho = 0.46 and 0.48, $P < 0.001$), itHBV-DNA (Rho = 0.49 and 0.59, $P < 0.001$) and pgRNA (Rho = 0.74 and 0.45, $P < 0.001$ and 0.004). Conversely, weaker correlations were found for qHBsAg with cccDNA (Rho = 0.31, $P = 0.007$), itHBV-DNA (Rho = 0.39; $P = 0.001$) and pgRNA (Rho = 0.13, $P = 0.43$). By AUROC, the best performance to predict a limited HBV reservoir was observed for the combination of serum HBV DNA < 20,000 IU/ml, HBcrAg < 2.0 log IU/ml and HBsAg < 3.2 log IU/ml (75% positive-predicted value and 95% specificity). Furthermore, the combined quantification of serum HBcrAg > 4.3 U/ml and HBV-DNA > 5.3 IU/ml identified pts with an Ishak $\geq$ 3 with 78% positive-predictive value and 97% specificity.

Conclusions: The combined evaluation of serum HBV-DNA, HBsAg and HBcrAg strongly correlate with the burden and productivity of intrahepatic HBV reservoir. HBcrAg, combined with HBV-DNA, also show to be a good peripheral marker to predict liver fibrosis stage. The combination of these serological parameters could be utilized to evaluate disease progression and to inform treatment decisions particularly in those patients with HBV DNA < 20,000 IU/ml.

https://doi.org/10.1016/j.dld.2018.01.026

OC-23

Impaired renal function but high sustained virological response (SVR) rates in hepatitis C virus (HCV) elderly treated with direct-acting antivirals (DAA): A report from the Lombardy Network

R. D'Ambrosio[1], L. Pasulo[2], A. Aghemo[3], M. Puoti[4], S. Zaltron[5], F. Maggiolo[6], G. Rizzardini[7], S. Fargion[8], P. Sacchi[9], R. Gulminetti[9], M. Zuin[10], T. Quirino[11], M.G. Rumi[12], A. Pan[13], P. Grossi[14], A. Rossini[15], A. Corbellini[16], C. Uberti Foppa[17], A. Colli[18], P. Lampertico[1], S. Fagiuoli[2], on behalf of the NAVIGATOR II study group

[1] *CRC "A. M. e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[2] *Gastroenterology, ASST Papa Giovanni XXIII, Italy*
[3] *Humanitas University Department of Biomedical Sciences, Rozzano-Milan, Italy*
[4] *Infectious Diseases ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[5] *Infectious Diseases, Spedali Civili, Brescia Bergamo, Italy*
[6] *Infectious Diseases, ASST Papa Giovanni XXIII, Bergamo, Italy*
[7] *Infectious Diseases, Sacco Hospital, Italy*
[8] *Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[9] *Infectious Diseases, Policlinico Pavia, Italy*
[10] *Gastroenterology, San Paolo Hospital, Milan, Italy*
[11] *Infectious Diseases, Busto Arsizio Hospital, Varese, Italy*
[12] *Hepatology, San Giuseppe Hospital, Milan, Italy*
[13] *Infectious Diseases Cremona Hospital, Italy*
[14] *Infectious Diseases Varese Hospital, Italy*
[15] *Hepatology, Spedali Civili, Brescia Bergamo, Italy*
[16] *Infectious Diseases Vizzolo Predabissi Hospital, Italy*
[17] *Immunology and Infectious Diseases, San Raffaele Hospital, Milan*
[18] *Internal Medicine, Lecco Hospital, Lecco*

Background and aims: Elderly hepatitis C virus (HCV) patients may benefit from direct-acting antivirals (DAA)-based regimens. Since these patients may be at risk of impaired renal function, we assessed DAA impact on kidney function in elderly HCV patients.

Material and methods: Between 2014 and 2017, 80% out of 5511 patients (63% males, median age 61, 61% cirrhotics) from 34 Hepatologic Centres in Lombardy had complete kidney function data: baseline, end-of-treatment (EOT), 12-week follow-up (SVR12). Estimated glomerular renal function (eGFR) was assessed

according to MDRD formula, and chronic kidney disease (CDK) according to KDIGO classification.

Results: Of the 4392 included patients, 817 (19%) were aged ≥75 years. Compared to younger patients, they were mostly females (57%, $p < 0.0001$), HCV-1 (67%, $p < 0.0003$), cirrhotics (71%, $p < 0.0001$) and low-weighted ($p < 0.0001$). They had more severe CKD (stage 1 28%, 2 54%, 3 17%, 4 1%; $p < 0.01$), with lower baseline MDRD [<75 vs. ≥75: 90 (14–264) *vs.* 78 (7–228) ml/min; $p < 0.0001$] but not creatinine ($p = 0.65$) values.

Elderly were mostly treated with RBV- and SOF-free regimens ($p < 0.0001$ and $p = 0.0008$, respectively).

At EOT, both younger and elderly patients showed lower-than-baseline eGFR (<75 *vs.* ≥75: $p < 0.0001$ *vs.* 0.02). At EOT elderly *vs.* younger displayed lower MDRD ($p = 0.0001$) but also creatinine ($p = 0.003$) values, as well as at SVR12 ($p < 0.0001$ and $p = 0.002$, respectively).

SOF-based or RBV-containing regimen did impact on EOT eGFR in younger patients ($p = 0.005$ and $p < 0.0001$, respectively) but not in elderly ($p = 0.07$ and $p = 0.07$, respectively). A sustained virological response (SVR) was achieved by 96%, independently on age ($p = 0.41$) and renal function ($p = 0.28$).

Conclusions: Elderly patients are at higher risk of impaired renal function before and during DAA treatment, independently on the used anti-HCV regimen, however without impacting on SVR rates.

https://doi.org/10.1016/j.dld.2018.01.027

OC-24

Sarcopenia predicts survival in patients with advanced hepatocellular carcinoma treated with sorafenib

G. Antonelli [1], E. Gigante [1], M. Iavarone [2], P. Begini [1], A. Sangiovanni [2], E. Iannicelli [3], P. Biondetti [6], A.M. Pellicelli [4], L. Miglioresi [4], P. Marchetti [5], P. Lampertico [2], M. Marignani [1]

[1] *Digestive and Liver Disease Unit, Sapienza University of Rome, Sant'Andrea University Hospital, Rome, Italy*
[2] *A.M. & A. Migliavacca Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Maggiore Hospital, University of Milan, Milan, Italy*
[3] *Radiology Unit, Sant'Andrea University Hospital, School of Medicine and Psychology, "Sapienza" University of Rome, Italy*
[4] *Liver Unit, San Camillo Forlanini Hospital, Rome, Italy*
[5] *Oncology Unit, Sant'Andrea University Hospital, "Sapienza" University of Rome, Italy*
[6] *Division of Radiology, Fondazione IRCCS Ca' Granda Maggiore Hospital, Milan*

Introduction: Sarcopenia, a condition characterized by muscle wasting, has been associated with poor outcomes in patients with cirrhosis and solid tumors. We analyzed influence of sarcopenia on survival of patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib, the standard of care for this stage.

Methods: We conducted a multicenter, retrospective study on 96 patients with advanced HCC treated with sorafenib. Patients with an abdominal computed tomography (CT) scan within 30 days from treatment start were enrolled. Data on pre-treatment anthropometric features, baseline laboratory findings, toxicity, treatment duration and overall survival (OS) were collected. Transverse CT images corresponding to third lumbar vertebrae (L3) were collected to calculate skeletal muscle index, defining presence of sarcopenia.

Results: In our cohort, patients were mainly males (78%) and sarcopenia was present in 49% of patients, with significant major prevalence in women (M 37.3% vs F 90.5% $p = 0.00001$). Patients were divided into two groups according to sarcopenia and compared: age was significantly higher in the sarcopenic group [66 years (31–87) *vs* 72 years (30–84)], while all other baseline features were similar, without significant difference in albumin levels, INR, body max index, serum sodium, creatinine, bilirubin and MELD score. Patients with sarcopenia showed a significantly shorter OS [39 (95% CI 26–50) *vs* 61 (95% CI 47–77) weeks ($p = 0.02$)], as well as time on treatment of sarcopenic patients [12.3 (95% CI 8–19) vs 25.9 (95% CI 15–33) weeks], while no significant differences in cause of drug interruption were detected. At multivariate analysis, sarcopenia was found to be an independent predictor of reduced OS ($p = 0.028$), and of a reduced time on treatment ($p = 0.0032$).

Conclusions: Sarcopenia measured with CT-scan is present in nearly half of patients with advanced HCC, and it can be used as a predictor of mortality and worse response to sorafenib.

https://doi.org/10.1016/j.dld.2018.01.028

OC-25

Clinical significance of time related fluctuations of AFP and PIVKA-II serum levels in patients with cirrhosis undergoing surveillance for hepatocellular carcinoma

G. Ricco [1], C. Cosma [2], G. Bedogni [3], A. Biasiolo [4], M. Guarino [5], P. Pontisso [4], F. Morisco [5], F. Oliveri [1], D. Cavallone [1], F. Bonino [3,6,7], M. Plebani [2], M.R. Brunetto [1,8]

[1] *Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Reference Center of the Tuscany Region for Chronic Liver Disease and Cancer, University Hospital of Pisa, Pisa, Italy*
[2] *Department of Laboratory Medicine, University-Hospital of Padua, Padua, Italy*
[3] *Italian Liver Foundation (Fondazione Italiana Fegato, FIF) Science Park, Campus Basovizza, Trieste, Italy*
[4] *Department of Internal Medicine, University of Padua, Padua, Italy*
[5] *Gastroenterology Unit, Department of Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy*
[6] *Institute of Biostructure and Bioimaging, National Research Council, Naples, Italy*
[7] *University of Pittsburgh Medical Center Institute for Health, Chianciano Terme, Siena, Italy*
[8] *Internal Medicine, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*

Introduction: The clinically meaningful variations of circulating HCC biomarkers in the single patient are uncertain. We studied the dynamics of AFP and PIVKA-II in 2–3 consecutive sera obtained at random time points in cirrhotic patients with and without HCC.

Materials and methods: AFP and PIVKA-II were measured in 1163 sera of 418 cirrhotics (31.1% HBV, 58.6% HCV, 10.3% non-viral) undergoing ultrasound HCC surveillance at 3 centres: 124 developed HCC (29 with 1 and 95 with 2 sera before the serum at diagnosis), 294 remained HCC-free for at least 12 months after the last specimen (2 sera in 62 and 3 sera in 232). Tests were performed

in a single laboratory using automated chemiluminescent-enzyme-immunoassays (Fujirebio, Tokyo, Japan). Time between time-points (t1, t2, t3) was expressed in months. AFP/PIVKA-II time-related changes were analysed by calculating the month-related variation coefficients (MVC = $\{[(xt_{last} - xt_{first})/xt_{first}] \times 100\}/(t_{last} - t_{first})$) and using a random-effect generalized least squares (RE-GLS) regression model.

Results: Multiple time-related ROC curve analysis of MVC shows 6 months (±1.5) as best time frame for both biomarkers. Using 10% MVC as cut-off the sensitivity/specificity for HCC diagnosis were 17.8/96.3% and 27.7/93.8% for AFP and PIVKA-II, respectively. Log_{10} AFP time-related (1–6 months) changes estimated by RE-GLS ranged between 1.06 and 1.19 (95%CI 0.72–1.63) and 0.87–1.16 (95%CI 0.92–1.45) for HCC+ and HCC−, whereas the values of log_{10} PIVKA-II were 1.07–1.18 (95%CI 0.75–1.39) and 1.01–1.05 (95%CI 0.93–1.16), respectively. In HCC-patients AFP was influenced by disease activity and showed more variability than PIVKA-II. The gap of median MVC between HCC+ and HCC− was up to six-fold higher for PIVKA-II than AFP.

Conclusion: The month-related variation coefficient (MVC) of AFP and PIVKA-II appears a reliable measure for individualized HCC surveillance with an optimal time frame [6(±1.5) months] coincident with the suggested timing of ultrasound surveillance. A 10% MVC cut-off for both biomarkers qualifies as a candidate diagnostic tool worth to be tested in prospective studies.

https://doi.org/10.1016/j.dld.2018.01.029

OC-26

Pathobiological and radiomic approach for hepatocellular carcinoma subclassification

F. Vasuri [1], M. Renzulli [2], S. Fittipaldi [1], L. Bolondi [3], R. Golfieri [2], A. D'Errico [1]

[1] *Pathology Unit, S. Orsola-Malpighi Hospital, Bologna University, Bologna, Italy*
[2] *Radiology Unit, S. Orsola-Malpighi Hospital, Bologna University, Bologna, Italy*
[3] *Internal Medicine, S. Orsola-Malpighi Hospital, Bologna University, Bologna, Italy*

Introduction: The classic histopathological features of hepatocellular carcinoma (HCC) are still inadequate in determining patient's prognosis.

Aims: (i) To improve HCC classification, including a better definition of advanced HCCs, with a multidisciplinary approach beyond morphology; (ii) to identify the radiological features distinctive of the "histologically-advanced" HCCs.

Materials and methods: Histopathological analysis, immunohistochemistry for CD34 and Nestin, and reverse transcriptase-polymerase chain reaction (RT-PCR) for TGFβ1 and IGF1R mRNA were performed on 96 HCCs for the identification of different morpho-vascular patterns; 740 miRNAs were analyzed on 22 HCCs by means of microfluidic cards; histopathological and magnetic resonance imaging (MRI) data of 39 liver nodules were correlated.

Results: Four distinct morpho-vascular HCC patterns had been identified at pathology: (A) microtrabecular with CD34-positive Nestin-negative sinusoids; (B) microtrabecular with CD34-positive Nestin-positive sinusoids; (C) with macrotrabeculae covered by CD34-positive Nestin-positive endothelium; (D) solid HCCs with CD34-positive Nestin-positive new-formed arteries. At RT-PCR a significant increase in TGFβ1 and IGF1R mRNA was found between pattern A and the other patterns. Moreover, each pattern correlated with a peculiar miRNA expressions.

On MRI, pattern A HCCs were isointense in 50% of cases on T1-weighted images (WI) and in 57% on T2-WI. Pattern B HCCs were hyperintense on T1-WI in two-third of cases, radiological features of "glycogen nodules", without hyperintensity on T2-WI. Pattern D HCCs were isointense on T1-WI in 83% of cases and hyperintense on T2-WI in 50%, all detected by typical vascular pattern on MRI. Pattern C HCCs showed the highest heterogeneity.

Conclusions: Our multidisciplinary approach allowed us to identify different morphological and vascular HCC types, each of them characterized by different expression of growth factors and miRNAs, and with peculiar MRI features too. While pattern A HCCs represent the "early" phase of hepatocarcinogenesis, pattern D could be recognized as advanced malignancies that skip the regenerative-dysplastic-neoplastic pathway.

https://doi.org/10.1016/j.dld.2018.01.030

OC-27

Loss of hepatic RuvBL1 accelerates DEN-induced carcinogenesis due to chronic liver damage and regeneration

M. Materozzi [2], F. Zanieri [1], E. Ceni [1], S. Polvani [1], M. Tarocchi [1], O. Bereshchenko [3], A. Galli [1], T. Mello [1]

[1] *Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy*
[2] *Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy*
[3] *Faculty of Medicine, University of Perugia, Perugia, Italy*

Recently, RuvBL1 has been receiving increasing consideration as a target for anti-cancer therapies. It is overexpressed in several human tumours including HCC and its expression correlates with a worse prognosis. Despite the growing body of data from *in vitro* models shows that RuvBL1 supports cancer cell growth through multiple mechanisms, whether it participates in the oncogenic transformation *in vivo* remains open to speculation. To address this question, we realized a hepatocyte-conditional RuvBL1 knock-out mouse model and evaluated HCC development after DEN injection.

$RuvBL1^{hep-/-}$ mice were generated by crossing RuvBL1-floxed with Albumin-Cre mice. HCC was induced by i.p. injection of DEN (5 mg/kg) at 14 days of age. HCC progression was monitored after 3, 6, 9 and 12 months. $RuvBL1^{hep-/-}$ mice were crossed with $B6^{mT/mG}$ mice to obtain a progeny in which mature (Alb^+, $RuvBL1^{-/-}$, $EGFP^+$) and non-mature (Alb^-, $RuvBL1^{wt/wt}$, $mTRed^+$) hepatocytes could be traced *in vivo*.

Contrary to our expectation, DEN-induced cancerogenesis was strikingly increased in $RuvBL1^{hep-/-}$ *vs* floxed mice. RuvBL1 deletion resulted in hepatocellular damage, apoptosis and compensatory proliferation. The liver damage induced by RuvBL1 deletion peaked around 2 weeks of age. Starting at 3 weeks of age, massive proliferation of non-mature hepatocytes and partial recovery of RuvBL1 protein levels were observed. Further characterization revealed that non-mature hepatocytes origin from $CK19^+CD133^+HNF4^+$ cells. We established that cycles of RuvBL1 deletion, hepatocytes loss and compensatory proliferation occurs throughout the lifetime of cKO mice.

This is the first report highlighting the essential role of RuvBL1 for hepatocyte survival and the impact of its loss on liver carcinogenesis. The increased HCC incidence does not reflect a tumor-suppressor role of RuvBL1, rather, it is the outcome of a chronic regenerative process involving staminal precursors. This

model may prove useful to investigate the mechanism underlying liver regeneration in the context of chronic hepatic damage.

https://doi.org/10.1016/j.dld.2018.01.031

OC-28

Functional characterization of a novel genetic variant predisposing to hepatocellular carcinoma development in nonalcoholic fatty liver disease

G.A. Baselli[1], M. Longo[1], M. Meroni[1], S. Pelusi[1], A.L. Fracanzani[1,2], G. Soardo[7], E. Bugianesi[3], R. Romagnoli[4], S. Petta[5], L. Miele[6], R. De Francesco[7], S. Fargion[1,2], P. Dongiovanni[2], L. Valenti[1,2]

[1] *Department of Pathophysiology and Transplantation, Università Degli Studi Di Milano, Milano, Italy*
[2] *Internal Medicine and Metabolic Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy*
[3] *Division of Gastroenterology, Department of Medical Sciences, A.O.U. Città della Salute e della Scienza, Università di Torino, Torino, Italy*
[4] *Liver Transplant Center, General Surgery 2U, AOU Città della Salute e della Scienza di Torino, University of Torino, Turin, Italy*
[5] *Section of Gastroenterology, Dipartimento Biomedico di Medicina Interna e Specialistica, University of Palermo, Palermo, Italy*
[6] *Institute of Internal Medicine and Gastroenterology Area, Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del S. Cuore, Largo Gemelli, 00168 Rome, Italy*
[7] *Istituto Nazionale di Genetica Molecolare INGM, Romeo ed Enrica Invernizzi, Milano*

Introduction: Nonalcoholic fatty liver disease (NAFLD) represents an emerging cause of hepatocellular carcinoma (HCC) and inherited factors are known to modify its progression. We performed whole exome sequencing on 72 Italian NAFLD-HCC patients and 50 healthy individuals to highlight novel HCC predisposing mutations. The rs141490768 in Interferon regulatory factor 3 (IRF3) resulted enriched in HCCs compared with European population (OR = 37.1, $p = 4.5 \times 10^{-7}$) and absent in controls. IRF3 is involved in interferons production in response to inflammatory stimuli. The rs141490768 encodes a loss-of-function variant (A418T) in the IRF3 inhibitory isoform IRF3-CL, suggesting that increased IRF3 activity may predispose to NAFLD-HCC.

Aim: To examine IRF3 role in NAFLD-HCC and whether IRF3 pathway inhibition by Amlexanox contrasts HCC growth.

Methods: Hepatic expression of IRF3 and IRF3-CL was evaluated by RT-qPCR in 87 bariatric patients.

IRF3 expression in HCC vs control tissue was assessed using RNASeq data (TCGA public dataset) of 20 NAFLD/cryptogenic-HCC patients.

IRF3 immunohistochemistry (IHC) was performed in 21 NAFLD patients stratified by disease severity.

HepG2 cells were exposed to 0.5 mM free fatty acids (FFAs), 100 μM Amlexanox, 10 μM Sorafenib or both.

Results: In bariatric patients, IRF3-CL/IRF3 was reduced in NASH patients compared to those with simple steatosis ($p < 0.05$), and inversely correlated with serum ALT and AST ($p < 0.05$), suggesting activation of the pathway during steatohepatitis. Consistently, IHC showed IRF3 nuclear localization in hepatocytes in NASH and not in steatosis. In TCGA patients, IRF3 was overexpressed in HCC ($p < 0.001$). Consistently, IHC showed a high IRF3 expression in NAFLD-HCC samples.

HepG2 exposure to FFAs increased IRF3 phosphorylation ($p < 0.05$). Moreover, Amlexanox treatment reduced cell proliferation ($p < 0.01$) and more so the combination of Amlexanox and Sorafenib ($p < 0.01$).

Conclusions: Results suggest IRF3 activation during steatosis progression to NASH and transition to HCC, representing an attractive therapeutic target, and highlight FFAs as a trigger for IRF3 activation in hepatocytes.

https://doi.org/10.1016/j.dld.2018.01.032

OC-29

Modulation of the NLRP3 inflammasome pathway mediates the anti-inflammatory action of indoleamine dioxygenase in experimental NASH

E. Vivoli, B. Piombanti, F. Marra

Dipartimento di Medicina Sperimentale e Clinica, Università di Firenze, Italy

Background and aims: The inflammasome pathway is implicated in the pathogenesis of NAFLD, but its regulatory mechanisms are only partially understood. Indoleamine 2,3-dioxygenase (IDO-1), generates kynurenine degrading tryptophan, and is involved in immune regulation and tolerance. In this study, we analyzed the possible cross-talk between the IDO and inflammasome pathways in the setting of experimental NASH.

Methods: In mice, steatohepatitis was induced by feeding for 4 weeks a diet deficient in methionine and choline (MCD), with or without administration of 1-methyl-D-triptophan (1MT, 5 mg/ml), an inhibitor of IDO. Cultured RAW264.7 murine macrophages were used for in vitro experiments.

Results: Inhibition of IDO with 1MTwas associated with increased expression of proinflammatory genes, including CCL2, IL-1beta, and iNOS. In addition, 1MT treatment was associated with downregulation of components of the NLRP3 inflammasome, including NLRP3, ASC, and IL-1beta. RAW264.7 were treated with low-dose LPS together with 1MT to inhibit IDO. In these conditions, IDO inhibition was associated with up-regulated secretion of IL-1beta, and increased expression of NLRP3 inflammasome components.

Conclusions: We demonstrate the novel interaction between the IDO pathway and NLRP3 inflammasome in murine macrophages and in a mouse model of steatohepatitis. This cross-talk may contribute to explain the complex inflammatory picture observed in NASH.

https://doi.org/10.1016/j.dld.2018.01.033

OC-30

Bile acid composition modulates insulin resistance in non-diabetic patients with NAFLD

C. Rosso[1], R. Younes[1], M. Eslam[2], F.W. Chen[2], M. Cucco[1], M. Gaggini[3], S. Coulter[2], F. Carli[3], C. Barbieri[3], V. della Latta[3], M.L. Abate[1], G.M. Saracco[1], A. Gastaldelli[3], J. George[2], E. Bugianesi[1]

[1] *Division of Gastroenterology, Department of Medical Sciences, University of Turin, Turin, Italy*
[2] *Storr Liver Centre, The Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Australia*
[3] *Cardiometabolic Risk Unit, Institute of Clinical Physiology, CNR, Pisa, Italy*

Introduction: Bile acids (BAs) are signaling molecules involved in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). BAs can modulate both glucose and lipid metabolism in insulin resistance (IR), a major pathogenic mechanism for the progression to non-alcoholic steatohepatitis (NASH). However, the association between BAs composition and insulin sensitivity (IS)/IR has been not fully investigated yet.

Aim: To assess the relationship between BAs composition and sites and mechanisms of IR in non-diabetic NAFLD patients.

Materials and methods: 41 patients with biopsy-proven NAFLD were studied. Plasma BAs composition was assessed by GC–MS. Adipose tissue IR (AT-IR), Hepatic IR (Hep-IR) and glucose clearance (GC) were derived from tracer studies. Visceral fat (VF) was assessed by NMR. Liver histology was scored according to Kleiner.

Results: Plasma levels of total primary BAs correlated with waist circumference (WC) ($r = 0.378$, $p = 0.014$), VF ($r = 0.406$, $p = 0.023$) and fasting C-peptide ($r = 0.301$, $p = 0.056$,). Among primary BAs, GCA directly correlated to WC ($r = 0.364$, $p = 0.019$), VF ($r = 0.383$, $p = 0.033$) and AT-IR ($r = 0.367$, $p = 0.018$) while TCDCA correlated with WC ($r = 0.334$, $p = 0.033$), VF ($r = 0.349$, $p = 0.05$), insulin secretion (C-peptide) ($r = 0.505$, $p = 0.001$), AT-IR ($r = 0.393$, $p = 0.014$), Hep-IR ($r = 0.331$, $p = 0.042$) as well as with hepatic steatosis and was inversely related to GC ($r = -0.304$, $p = 0.05$). UDCA had no correlation with metabolic parameters while TUDCA was significantly correlated with WC ($r = 0.339$, $p = 0.03$), C-peptide ($r = 0.390$, $p = 0.012$), AT-IR ($r = 0.374$, $p = 0.016$), Hep-IR ($r = 0.467$, $p = 0.002$) and liver fat.

Conclusions: In NAFLD patients, GCA, TCDCA and TUDCA are increased proportionally to IR at the main sites of insulin action (adipose tissue, liver and muscle) irrespective of diabetes. Since TCDCA is the most potent endogenous agonist of FXR, which upon activation improves insulin sensitivity, and TUDCA treatment in obese individuals has been found to improve insulin sensitivity, these increases may represent compensatory mechanisms to IR.

Funded by: Horizon2020 under grant agreement no.634413 for project EPoS.

https://doi.org/10.1016/j.dld.2018.01.034

OC-31

Berberis aristata, *Elaeis guineensis* and *Coffea canephora* extracts modulates the microRNA-122 expression and improves hepatic steatosis in mice fed high fat diet

V. Lembo[1], P. Mirra[2], G. Mazzone[1], A. Rossi[1], G. D'Argenio[1], V. Cossiga[1], C. Nigro[2], C. Miele[2], F. Beguinot[2], N. Caporaso[1], F. Morisco[1]

[1] *Department of Clinical Medicine and Surgery, Gastroenterology Unit, University of Naples "Federico II", Naples, Italy*
[2] *URT-GDD, National Council of Research & Department of Translational Medical Sciences, University of Naples "Federico II", Naples, Italy*

Background and aims: Nonalcoholic fatty liver disease (NAFLD) is common worldwide. MicroRNA-122 (miR-122) is involved in lipid metabolism and its role in liver diseases is emerging. A reduction in hepatic miR-122 expression has been reported in hepatic steatosis. The aims of this study were to evaluate the effects of a mixture of plant extracts consisting of *Berberis aristata*, *Elaeis guineensis* and *Coffea canephora* on the modulation of hepatic miR-122 levels and on the regression of hepatic steatosis in an animal model of NAFLD induced by a high fat diet.

Methods: Three groups of C57BL/6 mice ($n = 8$ each) were randomized into one of the following 24 week diets: (1) standard diet (SD, 3% fat); (2) high fat diet (HFD, 60% fat); (3) HFD enriched with plant extract (HFD + E) (140 mg/kg/die). Hepatic histology was examined by H&E staining. Alanine-aminotrasferase (ALT), total cholesterol (TC) and low-density lipoprotein cholesterol (LDLC) levels were measured in serum samples. Total RNA was isolated from the liver of each mouse and miR-122 levels were evaluated by real-time PCR.

Results: HFD + E mice displayed a significant reduction of weight gain ($p < 0.001$) and serum ALT levels ($p < 0.01$) compared to HFD mice. H&E staining showed macro- and microvesicular steatosis with ballooning degeneration in mice fed HFD, which is improved in mice fed HFD + E. Both TC and LDLC were decreased in HFD + E mice compared to HFD mice ($p < 0.001$). Moreover, HFD + E mice showed a rescue of hepatic miR-122 levels ($p < 0.05$), found to be decreased in HFD mice compared to SD mice ($p < 0.05$).

Conclusion: In conclusion, these results showed that a decrease of hepatic miR-122 levels is associated with hepatic steatosis in C57BL/6 mice fed with a HFD. The combination of *Berberis aristata*, *Elaeis guineensis* and *Coffea canephora* added to HFD improves hepatic steatosis, significantly reduces serum ALT levels, ameliorates lipid profile and this is associated with an increase of hepatic miR-122 levels.

https://doi.org/10.1016/j.dld.2018.01.035

OC-32

Metabolomics in the progression of non alcoholic fatty liver disease

J. Troisi [1,2], M. Masarone [1], A. Aglitti [1], C. Di Zenzo [1], V. Rosato [1], M. Persico [1]

[1] *Internal Medicine and Hepatology Division, Department of Medicine and Surgery "Scuola Medica Salernitana", University of Salerno, Salerno, Italy*
[2] *Theoreo srl – Spin-off company of the University of Salerno, Salerno, Italy*

Introduction: Non-alcoholic-fatty-liver-disease (NAFLD) encompasses a wide spectrum of diseases that range from simple steatosis (NAFL) to steatosis with inflammation and fibrosis (namely non-alcoholic steatohepatits or NASH) up to cirrhosis and hepatocellular carcinoma (HCC). The greatest challenge in this field is to recognize the patient with a more severe and/or progressive pathology. A reliable noninvasive method based on biomarkers does not exist. Metabolomics is a novel and powerful method to discover biomarkers and gives insights on diseases pathophysiology. Few studies have applied this technique to NAFLD patients.

Aims: To apply metabolomics to understand if simple steatosis, steatohepatitis and hepatocellular carcinoma occurred in NAFLD patients have a peculiar metabolites profile that can differentiate them among each others and from healthy controls.

Methods: Metabolomics signatures were obtained, by means of mass spectrometry gas chromatography, from 78 NAFLD patients of whom 58 diagnosed by liver biopsy (42 simple steatosis, 16 NASH) and 20 by clinical, laboratory and instrumental signs (15NASH-cirrhosis, 5-NASH-HCC), and from 67 age and sex matched healthy controls from a local blood bank.

Results: A statistical analysis with the "Partial Least Square Discriminant Analysis" (PLS-DA) was used to reveal class separation in metabolomics profiles between patients and controls and among each class of NAFLD, and to reveal the metabolites principally contributing to class differentiation. PLS-DA score plot showed a significant differentiation between NAFLD patients and controls ($R^2 = 0.822$, $Q^2 = 0.743$, $P < 0.001$), and also among the various clinical presentations of NAFLD ($R^2 = 0.782$, $Q^2 = 0.698$, $p < 0.05$). In particular: Glycocholic acid, Taurocholic acid, Phenylalanine and branched-chain amino acids increased at the increase of the severity of the disease from simple steatosis to NASH, NASH-cirrhosis and HCC while glutathione decreased (ANOVA multiple comparisons with Tukey HSD correction $p < 0.001$ for each).

Conclusion: These preliminary results suggest that metabolomics profiles of NAFLD patients could be an useful tool to non-invasively diagnose NAFLD and discriminate among the various stages of the disease, giving other insights into the pathophysiology of NAFLD.

https://doi.org/10.1016/j.dld.2018.01.036

OC-33

Role of SERPINB3 like serological and molecular biomarker into NASH development and progression

S. Maier [1], S.L. Crocè [2], M.R. Buonocore [2], C. Pilon [3], S. Fargion [4], R. Vettor [3], L.A. Sechi [1], D. Donnini [1], C. Pagano [3], L. Valenti [4], G. Soardo [1]

[1] *Liver Unit, Clinic of Internal Medicine, Department of Medical Area, University of Udine, Udine, Italy*
[2] *Clinica Patologie del Fegato, Internal Medicine Department, University of Trieste, Trieste, Italy*
[3] *Internal Medicine 3, Department of Medicine, University of Padua, Padua, Italy*
[4] *Department of Pathophysiology and Transplantation, Ca' Granda Ircss Foundation, Policlinico Hospital, University of Milan, Milan, Italy*

Background: NAFLD (non-alcoholic fatty liver disease) and NASH (non-alcoholic steatohepatitis) are emerging conditions that sequentially affect hepatocyte metabolism. Fibroblast Growth Factor 21 (FGF21) is produced by the liver and has autocrine and paracrine actions on liver energy metabolism while serpinB3 (SCCA) is produced by damaged liver cells and is considered a marker of progression to cirrhosis and hepatocellular carcinoma.

Aim of the study: A first aim of this study is to investigate expression profile of FGF21 and its receptor/coreceptor in liver biopsies of patients with NAFLD and NASH. A second aim is to assess whether circulating concentration of SCCA-IgM is increased in patients with NASH compared to patients with pure fatty liver.

Materials and methods: Expression of FGF21 and its receptor was measured by real-time PCR in liver biopsies of 42 patients with NAFLD/NASH and 16 matched controls. Moreover in a separate group of patients with NAFLD ($n = 39$) and NASH ($n = 45$) serum concentration of SCCA-IgM was measured.

Results: A significant lower expression of FGF21 (53 ± 3.1 u.a. vs 27.2 ± 1 u.a., $p < 0.05$), FGF21-R1 (4.7 ± 0.2 u.a. vs 2.7 ± 0.1 u.a., $p < 0.02$) and its coreceptor β-klotho (107.6 ± 6.4 u.a. vs 64.0 ± 1 u.a., $p < 0{,}03$) was found in patients with NAFLD/NASH. SCCA-IgM serum concentration was significantly increased in patients with NASH compared with those with NAFLD (9.2 ± 1.8 vs 31.0 ± 7.2 u.a./mL, $p = 0.007$).

Conclusions: Downregulation of FGF21, FGF21-R1 and β-klotho suggests that both low hormonal levels and its membrane receptor and coreceptor might contribute to detrimental metabolic effect in hepatocytes of NAFLD/NASH patients. Moreover higher circulating levels of SCCA-IgM in patients with NASH compared to those with pure fatty liver suggest that this protein might represent a possible marker of hepatic damage before the progression to cirrhosis and hepatocellular carcinoma.

https://doi.org/10.1016/j.dld.2018.01.037

OC-34

Impact of Proprotein Convertase Subtilisin/Kexin Type 7 genetic variation in patients with non-alcoholic fatty liver disease

P. Dongiovanni[1], M. Meroni[2], A. Cespiati[2], G.A. Baselli[2], R. Rametta[1], S. Pelusi[2], A. Fracanzani[1,2], S. Badiali[1], J. Pihlajamaki[3], S. Romeo[4], S. Petta[5], A. Craxi[5], V. Nobili[6], S. Fargion[1,2], L. Valenti[1,2]

[1] *Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy*
[2] *Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milano, Italy*
[3] *Department of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland*
[4] *Department of Molecular and Clinical Medicine, University of Gothenburg, Sweden*
[5] *Department of Gastroenterology, University of Palermo, Palermo, Italy*
[6] *Hepatometabolic Unit, Bambino Gesù Pediatric Hospital, Rome, Italy*

Background and aims: Inherited factors modify the risk of non-alcoholic fatty liver disease (NAFLD), steatohepatitis (NASH) and liver fibrosis by regulating hepatocellular lipid handling. Deregulation of iron and lipoprotein metabolism are typical features of NAFLD. The rs236918 G>C intron variant in the Proprotein Convertase Subtilisin/Kexin Type 7 (PCSK7) gene has been associated with liver fibrosis in hereditary hemochromatosis and its variation influences circulating lipid levels. Aim was to examine the impact of the rs236918 PCSK7 variant on iron metabolism, metabolic traits and liver disease in patients at risk of NASH.

Methods: We genotyped rs236918 in 1801 European NAFLD patients from the Liver Biopsy Cross-Sectional Cohort (LBC). Liver damage was assessed according to NAS, PCSK7 hepatic expression by qRT-PCR, protein and circulating levels by Western blot and ELISA respectively, in a subset ($n = 78$).

Results: The C allele was associated with higher transferrin saturation (Estimate: +4.82; 0.34–9.29; $p = 0.035$) and circulating triglycerides (Estimate: +0.09; 0.007–0.17; $p = 0.03$). Concerning liver damage, while it had no effect on steatosis and ballooning, the C allele was independently associated with more severe lobular inflammation at multivariate analysis (Table 1). However, this did not translate in more severe fibrosis. PCSK7 was more expressed in hepatocytes than in hepatic stellate cells ($p < 0.05$) and gene expression correlated with *de novo lipogenesis* ($p < 0.05$). The rs236918 variant affected hepatic expression levels of PCSK7 alternative mRNA transcripts. Furthermore, carriers of C allele showed increased PCSK7 protein in the liver and in the circulation compared to non-carriers ($p < 0.01$, $n = 72$), and circulating PCSK7 was correlated with serum triglycerides.

Conclusions: The PCSK7 rs236918 G>C variant may bridge hepatic inflammation with deregulation of iron metabolism and dyslipidemia in NAFLD patients. The mechanism may be related to increased PCSK7 protein levels, suggesting PCSK7 as a new therapeutic target for metabolic disorders.

Table 1
Impact of PCSK7 rs236918 variant on hepatic lobular inflammation in 1801 NAFLD patients from the LBC.

	Estimate	95%CI	*P adjusted
Age, yrs	−0.0008	−0.007 to 0.005	0.80
Sex, M	+0.17	0.07 to 0.27	0.001
BMI, Kg/m^2	−0.02	−0.03 to −0.01	0.0002
T2DM, yes	+0.33	0.22 to 0.44	<0.0001
PNPLA3, I148M	+0.42	0.29 to 0.56	<0.0001
TM6SF2, E167K	+0.28	0.03 to 0.54	0.03
MBOAT7, T allele	+0.10	−0.02 to 0.23	0.11
PCSK7, C allele	+0.22	0.02 to 0.42	0.03

https://doi.org/10.1016/j.dld.2018.01.038

Digestive and Liver Disease 50(1S) (2018) 20–41

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Abstracts of the 51st A.I.S.F. – Italian Association for the Study of the Liver – Annual Meeting 2018 Rome, February 22nd–23rd, 2018: Selected Posters Thursday

T-01

The course of oesophagogastric varices in patients with cirrhosis after DAA-induced HCV clearance

V. Calvaruso[1], I. Cacciola[2], S. Petta[1], G. Caccamo[2], E. Conte[1], M.G. Minissale[3], M. Licata[1], F. Simone[1], G. Squadrito[2], A. Licata[3], G. Raimondo[2], A. Craxì[1], V. Di Marco[1]

[1] *Gastroenterology and Hepatology Unit, DIBIMIS, University of Palermo, Italy*
[2] *Division of Clinical and Molecular Hepatology, University of Messina, Italy*
[3] *Internal Medicine Unit, DIBIMIS, University of Palermo, Italy*

Background and aims: Use of direct acting antivirals (DAAs) has allowed to clear HCV in almost all patients even in the presence of advanced cirrhosis. Although it has been suggested that cirrhotic portal hypertension may regress after SVR, the ultimate effect of HCV clearance on the development and progression of oesophagogastric varices (OV) is still unexplored. We assessed in a prospective cohort of patients with cirrhosis the evolution of endoscopic features of portal hypertension induced by SVR obtained with DAAs.

Method: 321 consecutive patients (mean age: 65.1 ± 10.5, males: 58%) with HCV Child-Pugh A cirrhosis treated with DAAs were enrolled between January 2015 and May 2016. All patients underwent esophagogastroscopy (EGS), liver ultrasound (US), liver stiffness measurement (LSM) by Transient Elastography and laboratory tests before the starting DAAs and after achieving SVR. LS * spleen diameter/platelet ratio (LSPS) was calculated as previously described [1].

Results: Forty-one patients were excluded from the analysis, 32(10%) since they had F2/F3 OV at baseline, and 9(2.8%) since they did not achieve SVR. Overall, 280 SVR patients were analysed. At baseline, 100 patients (35.7%) did not have OV and 180(64.3%) had small OV. None received beta-blockers. After a median time of 24.6 months EGS showed *de novo* development of OV in 24/100(24%) patients and progression from F1 to F2/F3 OV in 30/180 patients (16.7%), $p = 0.68$ by Kaplan–Meier. By Cox regression analysis, LSPS as continuum variable (HR: 1.06, CI95%: 1.01–1.11, $p = 0.025$) or at a cut off ≥ 3(HR: 3.16, CI95%: 1.64–6.09, $p = 0.001$) was associated with OV progression. Age ($p = 0.15$), gender ($p = 0.93$) and BMI ($p = 0.07$) did not correlate with progression of OV.

Conclusion: Progression of clinically significant portal hypertension, as assessed by the evolution of oesophagogastric varices, is not uncommon among patients with HCV cirrhosis after HCV clearance. Non-invasive evaluation using combined data of LS, spleen diameter, and platelet count can assist in identifying patients in whom portal hypertension is likely to progress notwithstanding SVR.

Reference

[1] Berzigotti A. Gastroenterology 2013;144:102–11.

https://doi.org/10.1016/j.dld.2018.01.079

T-02

HCV eradication by DAA improves glucose tolerance and reduces post-load insulin resistance in cirrhotic patients with genotype 1

F. Salomone[1], M. Catania[2], G. Bertino[3], J. Godos[4], G. Magrì[1], G. Li Volti[4], A. Montineri[4]

[1] *Gastroenterologia, Azienda Sanitaria Provinciale di Catania, Catania, Italy*
[2] *Patologia Clinica, Azienda Sanitaria Provinciale di Catania, Catania, Italy*
[3] *Medicina Clinica e Sperimentale, Università di Catania, Catania, Italy*
[4] *Scienze Biomediche e Biotechnologiche, Università di Catania, Catania, Italy*

Background and aims: Genotype 1 chronic hepatitis C (CHC) is associated with an impairment of glucose homeostasis, especially in the advanced stages of the disease. Glucose tolerance is an independent predictor of liver-related mortality in patients with cirrhosis due to CHC. However, no study has demonstrated so far weather HCV clearance affects glucose tolerance.

Methods: To this aim, we performed a prospective study assessing the effects of DAA treatment in non-diabetic cirrhotic patients with genotypes 1a/1b and impaired glucose tolerance (IGT) based on a 75-g oral glucose tolerance test (OGTT). IGT was diagnosed by a 2-h plasma glucose (PG) between 140 mg/dl and 199 mg/dl. Insulin resistance (IR) was estimated by the oral glucose insulin sensitivity (OGIS) index, an accurate OGTT-derived measure.

Results: After meeting the inclusion criteria, the study population included 32 outpatients (26/6 genotypes 1b/1a; age 62 ± 7.4 years; 18 males) with compensated Child-A cirrhosis. All patients achieved a sustained virologic response following DAA treatment. After viral eradication, we did not observe change in fasting PG (103.5 ± 7.1 vs 102.8 ± 7.2 mg/dl, $P = 0.15$) but 2-h PG was reduced (165.2 ± 22.7 vs 138.5 ± 21.3 mg/dl, $P < 0.001$). HCV eradication led also to a significant reduction of HbA1c (6.1 ± 0.2% vs 5.7 ± 0.3%, $P < 0.001$) and post-load IR as assessed by the OGIS index (6.92 ± 1.56 vs 9.52 ± 1.39 mg/kg/min, $P < 0.001$). These effects were observed despite no change in body mass index from baseline to follow-up (25.6 ± 4.3 vs 25.8 ± 4.4, $P > 0.5$).

Conclusions: Our results indicate that HCV eradication by DAA early improves glucose tolerance in patients with HCV-related cirrhosis.

https://doi.org/10.1016/j.dld.2018.01.080

T-03

Pre-treatment risk stratification in primary biliary cholangitis: A predictive model to guide first-line combination therapy

M. Carbone[1,2], A. Nardi[3], G. Carpino[4], V. Cardinale[6], H. Ainsworth[5], M. Heneghan[7], D. Thorburn[8], A. Bathgate[9], R. Jones[10], J.M. Neuberger[11], P.M. Battezzati[12], M. Zuin[12], S. Taylor-Robinson[13], M. Donato[14], J. Kirby[15], R. Mitchell-Thain[16], A. Floreani[17], F. Sampaziotis[18], L. Muratori[19], D. Alvaro[6], M. Marzioni[20], L. Miele[21], F. Marra[22], E. Giannini[23], E. Gaudio[4], V. Ronca[12], G. Bonato[2], L. Cristoferi[2], F. Malinverno[2], A. Gerussi[2], H.J. Cordell[24], G.M. Hirschfield[25], D. Stocken[5], G.J. Alexander[26], R.N. Sandford[1], D.E. Jones[27], P. Invernizzi[2], G.F. Mells[1], for the Italian PBC Study Group and UK-PBC Consortium

[1] *Academic Department of Medical Genetics, University of Cambridge, Cambridge, UK*
[2] *Division of Gastroenterology and Hepatology, Department of Medicine and Surgery, University of Milan Bicocca, Milan, Italy*
[3] *Department of Mathematics, Tor Vergata University of Rome, Rome, Italy*
[4] *Division of Health Sciences, Department of Movement, Human and Health Sciences, University of Rome "Foro Italico,", Rome, Italy*
[5] *Institute of Health & Society, Newcastle University, Newcastle, UK*
[6] *Department of Medico-Surgical Sciences and Biotechnologies, Polo Pontino, Sapienza University of Rome, Rome, Italy*
[7] *Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, UK*
[8] *Sheila Sherlock Liver Center, The Royal Free London NHS Foundation Trust, London, UK*
[9] *Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh, Edinburgh, UK*
[10] *Liver Unit, St James's University Hospital, Leeds, UK*
[11] *Liver Unit, Queen Elizabeth Hospital, Birmingham, UK*
[12] *Division of Internal Medicine and Liver Unit, Ospedale San Paolo, Milan, Italy*
[13] *Liver Unit, Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, Imperial College London, London, UK*
[14] *Gastroenterology and Hepatology Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy*
[15] *Applied Immunobiology and Transplantation Research Group, Institute of Cellular Medicine, Faculty of Medical Sciences, University of Newcastle, Newcastle upon Tyne, UK*
[16] *PBC Foundation, UK*
[17] *Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy*
[18] *Department of Surgery, Wellcome Trust-Medical Research Council Stem Cell Institute, Anne McLaren Laboratory, University of Cambridge, Cambridge, UK*
[19] *Liver Unit, Policlinico di Sant'Orsola-Malpighi, Bologna, Italy*
[20] *Clinic of Gastroenterology and Hepatology, Ospedali Riuniti University Hospital, Ancona, Italy*
[21] *Department of Internal Medicine and Gastroenterology, Gemelli University Hospital, Rome, Italy*
[22] *Department of Clinical and experimental Medicine, University of Florence, Florence, Italy*
[23] *Division of Gastroenterology, Department of Internal Medicine, IRCCS-Azienda Ospedaliera Universitaria San Martino-IST, Genova, Italy*
[24] *Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK*
[25] *Center for Liver Research and NIHR Biomedical Research Unit, University of Birmingham, Birmingham, UK*
[26] *Department of Medicine, University of Cambridge, Cambridge, UK*
[27] *Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK*

Introduction: EASL guidelines of PBC advocate selection of patients in needs for second-line therapies based on the UDCA response. This means that patients in greatest need of second-line therapy must wait, at least, 12 months to start it. An alternative, untested approach is to treat high-risk patients with combination therapy from the outset. The aim of this study was develop a predictive model of UDCA response that will enable baseline selection of patients at high-risk of inadequate response.

Methods: We analysed data on 2,703 patients from the UK-PBC Cohort. The endpoint was UDCA response (ALP < 1.67 × ULN after ≥12 months of UDCA). We derived the best-fitting model using logistic regression that underwent internal validation as well as external validation in an independent Italian cohort ($n = 460$). Finally, we explored correlations of the score with several histological features in an independent cohort ($n = 20$) for whom baseline FFPE liver biopsies were available.

Results: The following pre-treatment conditions were associated with greater probability of inadequate response to UDCA: higher ALP ($p < 0.0001$) and bilirubin ($p = 0.0003$), lower transam-

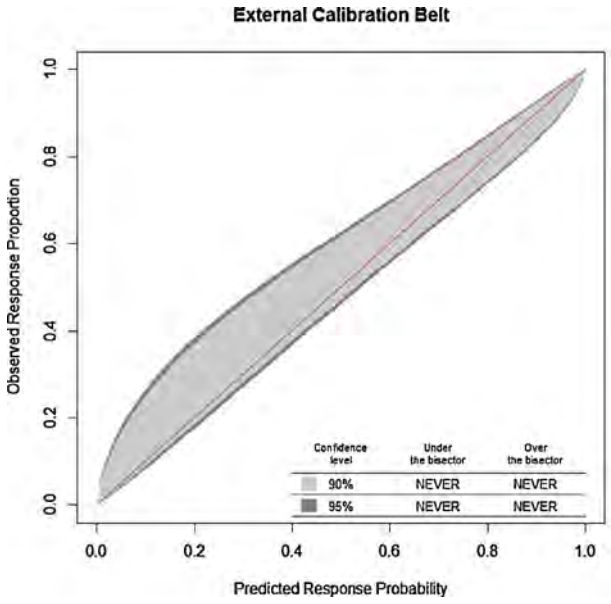


Fig. 1.

inases (TA, $p = 0.0012$), younger age ($p < 0.0001$), larger interval from diagnosis to starting UDCA (time-lag, $p < 0.0001$) and worsening of ALP from diagnosis to starting UDCA (ΔALP, $p < 0.0001$). Based on these, we derived a predictive score of UDCA response:

$$\text{UDCA response score (URS)} = 0.77 + 0.60 \times (\sqrt{\text{TB}})^{-1} - 2.73 \times \log(\text{ALP}) + 0.35 \times \log(\text{TA}) + 0.03 \times \text{age} - 0.15 \times (\text{time} - \text{lag}) - 0.56 \times \Delta\text{ALP}$$

In internal validation the AUROC was 0.87(0.86–0.89). In external validation the AUROC was 0.83(0.79–0.87) with a good calibration (Fig. 1). In PBC liver biopsies, the URS was inversely correlated with the extent of ductular reaction (DR) ($r = -0.56$, $p = 0.0130$) and extent of fibrosis ($r = 0.60$, $p = 0.0050$).

Conclusions: We derived and validated a model predicting future UDCA response prior to initiation of therapy. The URS correlated with the extent of DR and extent of fibrosis indicating that the score reflects the underlying pathologic process. A potential use for the URS is for pre-treatment selection of high-risk PBC patients for a clinical trial of primary versus sequential combination therapy. If the former is shown to achieve higher or faster rates of remission, the model may then be used for pre-treatment risk stratification in clinical practice.

https://doi.org/10.1016/j.dld.2018.01.081

T-04

The cancerogenic potential of primary human Cholangioracinoma cells is inhibited by Obeticholic Acid, a Farnesoid X Receptor (FXR) agonist

S. Di Matteo [1], L. Nevi [1], D. Costantini [1], M. Colantonio [1], F. Giulitti [1], C. Napoletano [2], S. Safarikia [1], E. Manzi [3], A.M. Derose [4], F. Melandro [5], M.C. Bragazzi [9], G. Grazi [3], P.B. Berloco [5], F. Giuliante [4], G. Carpino [6], V. Cardinale [9], E. Gaudio [7,8], D. Alvaro [9]

[1] *Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Italy*
[2] *Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy*
[3] *Gastroenterology Unit, Regina Elena National Cancer Institute, Rome, Italy*
[4] *Hepatobiliary Unit, Catholic University of the Sacred Heart School of Medicine, Rome, Italy*
[5] *Department of General Surgery and Organ Transplantation, Sapienza University of Rome, Rome, Italy*
[6] *Department of Movement, Human and Health Sciences, Division of Health Sciences, University of Rome "Foro Italico", Rome, Italy*
[7] *Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Sapienza University of Rome, Rome, Italy*
[8] *Division of Human Anatomy, Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Sapienza University of Rome, Italy*
[9] *Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy*

Cholangiocarcinoma (CCA) is enriched of cancer stem cells associated with aggressiveness and drug resistance. FXR, involved in neoplastic transformation of stem cells and/or cholangiocytes, is down-regulated in human CCA cells lines.

Our AIM was to evaluate, in primary cultures of human (hiCCA) the effects of the FXR agonist, obeticholic acid (OCA), on the cancerogenic potential of human CCA cells.

Primary cell cultures were prepared from mucin- or mixed-hiCCA subtypes from patients. The increasing concentrations (0–5 μM) of OCA were added to culture media and, after 3–10 days, their proliferation (MTS assay, population doubling time), apoptosis (AnnexinV-FITC/PI), cell migration and invasion (wound healing and Matrigel® invasion assay) and cancerogenic potential (spheroid formation, clonogenic assay, colony formation capacity) were evaluated.

FXR was downregulated (RT-qPCR) in iCCA vs normal hBTSCs ($p < 0.001$) and in mucin-iCCA vs mixed-iCCA ($p < 0.05$). OCA significantly ($p < 0.05$) inhibited proliferation of both mucin-iCCA and mixed-iCCA as low as the concentration of 0.05 μM (IC_{50} = 0.38 μM in mixed-iCCA; 2.1 μM in mucin-iCCA). CDCA inhibited cell proliferation, but lower than OCA, consistent with the different potency in FXR activation. The impairment of colony and spheroid formation capacity and delayed wound healing and Matrigel® invasion demonstrated that OCA significantly induced apoptosis of both the subtypes and decreased the *in vitro* cancerogenic potential of iCCA cells. In general, these effects were more evident against mixed- than mucin-iCCA cell. When administered together with gemcitabine and cisplatin, OCA potentiated the anti-proliferative and pro-apoptotic effects of these chemotherapeutics, but mainly on

mixed-iCCA and abolished the capacity of both iCCA-subtypes to form colonies.

FXR is down-regulated in iCCA cells, but its activation by OCA results in *in vitro* anti-cancerogenic effects against both mucin and mixed-iCCA human primary cell cultures. The effects of OCA predominate against mixed-iCCA, consistent with the lower aggressiveness and the higher FXR expression in this CCA subtype.

https://doi.org/10.1016/j.dld.2018.01.082

T-05

Adherence to EASL antibiotic treatment recommendations improves the outcomes of patients with cirrhosis and bacterial infections. Results from the ICA "Global Study"

S. Piano[1], V. Singh[2], P. Caraceni[3], R. Maiwall[4], C. Alessandria[5], J. Fernandez[6], E.C. Soares[7], D.J. Kim[8], S.E. Kim[9], M. Marino[10], J. Vorobioff[11], R. Ribeiro Barea[12], M. Merli[13], L. Elkrief[14], V. Vargas[15], A. Krag[16], S.P. Singh[17], L.A. Lesmana[18], C. Toledo[19], S. Marciano[20], X. Verhelst[21], F. Wong[22], N. Intagliata[23], L. Rabinowich[24], L.A. Colombato[25], S.G. Kim[26], A. Gerbes[27], F. Durand[28], J.P. Roblero[29], K.R. Bhamidimarri[30], T.D. Boyer[31], M. Maevskaya[32], E. Fassio[33], H.S. Kim[34], J.S. Hwang[35], A. Gadano[20], S.K. Sarin[4], P. Angeli[1], on behalf of the International Club of Ascites Global Study Group

[1] *Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine – DIMED, University of Padova, Padova, Italy*
[2] *Postgraduate Institute of Medical Education and Research, Chandigarh, India*
[3] *Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy*
[4] *Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India*
[5] *Division of Gastroenterology and Hepatology, AOU Città della Salute e della Scienza di Torino, University of Turin, Italy*
[6] *Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain*
[7] *Gastrocenter, University of Campinas, Campinas, Brazil*
[8] *Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Republic of Korea*
[9] *Department of Internal Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea*
[10] *Liver Unit, Hospital Dr. Carlos B. Udaondo, Buenos Aires, Argentina*
[11] *Universidad Nacional de Rosario, Rosario, Argentina*
[12] *Hepatologia, Hospital Regional de Mato Grosso do Sul (HRMS), Campo Grande, Brazil*
[13] *Gastroenterology, Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy*
[14] *Unit of Gastroenterology and Hepatology, University Hospital of Geneva, Geneva, Switzerland*
[15] *Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain*
[16] *Department of Medical Gastroenterology, Odense University Hospital, Odense, Denmark*
[17] *Department of Gastroenterology, Sriram Chandra Bhanj Medical College, Cuttack, India*
[18] *Digestive Disease & GI Oncology Center, Medistra Hospital, Jakarta, Indonesia*
[19] *Hospital Valdivia, Universidad Australe de Chile, Valdivia, Chile*
[20] *Liver Unit, Hospital Italiano, Buenos Aires, Argentina*
[21] *Department of Gastroenterology and Hepatology, Ghent University Hospital, Belgium*
[22] *Division of Gastroenterology, Department of Medicine, University of Toronto, Ontario, Canada*
[23] *Division of Gastroenterology and Hepatology, University of Virginia Health System, University of Virginia, Charlottesville, VA, USA*
[24] *Liver Unit, Department of Gastroenterology, Tel-Aviv Medical Center, Tel-Aviv, Israel*
[25] *Hospital Británico, Buenos Aires, Argentina*
[26] *Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea*
[27] *Liver Center Munich, Department of Medicine 2, University Hospital, LMU, Munich, Germany*
[28] *Hepatology & Liver Intensive Care, Hospital Beaujon, Clichy, France*
[29] *Universidad de Chile, Santiago, Chile*
[30] *Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA*
[31] *Department of Medicine, University of Arizona, Tucson, Arizona, USA*
[32] *University of Moscow, Moscow, Russia*
[33] *Liver Unit, Department of Medicine, Hospital Alejandro Posadas, Buenos Aires, Argentina*
[34] *Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Republic of Korea*
[35] *Department of Internal Medicine, Keimyung University College of Medicine, Daegu, Korea*

Introduction: Bacterial infections are a common cause of decompensation in patients with cirrhosis. On 2014, EASL recommendations for antibiotic treatment in patients with cirrhosis and bacterial infections were published. The effects of adherence to these recommendations have never been investigated so far.

Aim: To assess the clinical impact of the adherence to EASL recommendations in patients with cirrhosis and bacterial infections.

Methods: In the "Global Study", 1302 patients with cirrhosis and bacterial infection were enrolled. Demographic, clinical, microbiological and treatment data were collected at the diagnosis of infection and during the hospitalization. Patients were followed up until death, liver transplantation or discharge. The empirical antibiotic treatment was considered adherent to EASL recommendations if at least one of the antibiotic/combination recommended was administered.

Results: The antibiotic treatment was adherent to EASL recommendations in 61% of patients, while was broader in 14% and weaker in 25%. Northern American centers prescribed more frequently broader antibiotics (31vs13%; $p < 0.001$) while Northern European and Asian centers administered more frequently weaker ones (30vs21%; $p < 0.001$). Adherence to EASL recommendations was poorer in pneumonia (27vs71%; $p < 0.001$) and nosocomial infections (54vs64%; $p = 0.002$). In patients with positive cultures (57%), the administration of antibiotics weaker than those suggested by EASL recommendations resulted in lower antimicrobial

susceptibility (50vs75%; $p < 0.001$). However, bacteria isolated in Asian centers had a lower antimicrobial susceptibility to antibiotics suggested by EASL recommendations (58vs80%; $p < 0.001$), mainly due to a high prevalence of multi drug resistant bacteria (51vs28%; $p < 0.001$).

After adjusting for confounders (age, ACLF, quick SOFA and MELD-Na score), the administration of antibiotics weaker than EASL recommendations was associated with a higher risk to develop new organ failures (OR = 1.50; $p = 0.010$), septic shock (OR = 1.51; $p = 0.044$) and in-hospital mortality (OR = 1.47; $p = 0.034$).

Conclusions: The adherence to EASL recommendations was associated with better outcomes in patients with cirrhosis and bacterial infections and should be promoted. However, different empirical antibiotic strategies should be developed in certain countries due to the high prevalence of MDR bacteria.

https://doi.org/10.1016/j.dld.2018.01.083

T-06

The inhibitory effect of ADM on hepatic NF-κB activation in 2D and 3D hepatic cell cultures

S. De Martin [1], E. Caon [1,2], D. Gabbia [1], A. Floreani [3], G. Zigiotto [1], Z. Zhang [2], L. Frenguelli [2], W. Al-Akkad [2], S. Sarcognato [4], M. Guido [4], G. Mazza [2], M. Pinzani [2], K. Rombouts [2]

[1] *Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy*
[2] *Regenerative Medicine & Fibrosis Group, Institute for Liver and Digestive Health, University College London (UCL), London, UK*
[3] *Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy*
[4] *Department of Medicine, General Pathology and Cytopathology Unit, University of Padova, Padova, Italy*

The neuropeptide adrenomedullin (ADM) shows anti-inflammatory activity but its role has not been investigated in liver diseases. We assessed the hepatic ADM expression in different inflammatory liver diseases (HCV, AIH, NASH) and the mechanism(s) by which ADM affects NF-κB activation in classical 2D and a new 3D model.

Immunofluorescence analysis was performed on liver tissue to assess ADM expression and α-SMA colocalization. HepG2 and LX2 were exposed to LPS (1 ng/mL) for 24 h, or ADM (10^{-7}) for 4 h followed by LPS. ICC for p65 nuclear translocation and QRT-PCR was performed. Human liver 3D scaffolds were obtained by decellularization of healthy and cirrhotic livers. hHSCs were cultured on scaffolds for 10 days. Primary hHSC in healthy scaffolds were treated as above, or with LPS for 1–3 h, PDGF-BB (1–10 ng/mL), or TGFbeta1 (2–5 ng/mL) for 24 h. HSCs in cirrhotic scaffolds were exposed to ADM for 4 h. QRT-PCR was performed.

HSCs ADM-related fluorescence intensity in NASH patients ($n = 5$) was less than in HCV ($n = 5$) and AIH ($n = 5$) patients, but the degree of colocalization was similar. ADM pretreatment of LX2 and HepG2 in 2D reduced p65 nuclear translocation and increased IkBα gene expression. ADM gene expression decreased in TGFbeta1 and LPS-treated hHSCs cultured in 2D and was upregulated in 3D. In contrast, TGFbeta1 and PDGF-BB-treated hHSCs in 3D showed a reduced ADM expression. ADM pretreatment in hHSCs in healthy scaffolds increased ADM expression, reduced NFKB1 and completely abrogated the effect of subsequent exposure to all stimuli. ADM expression was upregulated in hHSCs in cirrhotic vs healthy scaffolds and exogenous ADM treatment favoured hHSCs deactivation in cirrhotic scaffolds.

ADM expression changes with respect to the aetiology of liver inflammation and leads to a reduction in activation of the canonical NF-κB pathway in hepatic cells. Therefore, the ADM system might be a possible pharmacological target for the management of inflammatory liver diseases.

https://doi.org/10.1016/j.dld.2018.01.084

T-07

Hepatic ischemic injury decreases using negative allosteric modulators of metabotropic glutamate receptor subtype 5

C. Berardo [1], V. Siciliano [1], L.G. Di Pasqua [1], P. Richelmi [1], F. Nicoletti [2], M. Vairetti [1], A. Ferrigno [1]

[1] *Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy*
[2] *Department of Physiology and Pharmacology, University La Sapienza, Roma, Italy*

The selective blockade of metabotropic glutamate receptor subtype 5 (mGluR5) with 2-methyl-6-(phenylethynyl) pyridine (MPEP), a negative allosteric modulator (NAM), improves the viability of anoxic hepatocytes. However, in microglia and astrocytes, MPEP reduced ATP production. Since ATP depletion is involved in the ischemic injury, we investigated the mechanism of MPEP-mediated ATP depletion, the protection mediated by other NAMs against ischemia and the liver functionality in an *ex-vivo* model of ischemia/reperfusion (I/R) injury.

Male Wistar rat hepatocytes were exposed to 90 min anoxia at 37 °C with MPEP and 3-((2-methyl-4-thiazolyl) ethynyl) pyridine (MTEP) at 3–30 μM, Fenobam (Fen) at 1-10-50-100 μM. Hepatocytes viability was evaluated by trypan blue exclusion and LDH release. Rat liver mitochondria were treated with MPEP, MTEP, Fen at 0.3-3-30 μM. Mitochondrial respiratory control ratio, membrane potential, ROS production and F_1F_O-ATPase activity were assessed. ATP was assessed in hepatocytes, mitochondria and in acellular buffers containing ATP and MPEP, MTEP, Fen. Wildtype and mGluR5 knockout livers from Balb-c mice were isolated, subjected to I/R and treated with MPEP 0.3 μM; LDH, AST and TNF-alpha release were evaluated.

MPEP 30 μM, MTEP 3 μM and Fen 50 μM improved significantly anoxic hepatocytes viability respect to anoxic controls. ATP was monitored before and after N_2 insufflation. MPEP significantly lowered ATP respect to oxygenated controls; MPEP-treated cells showed a slower decline in ATP after N_2 insufflation. The same trend was observed for MTEP but not for Fen. In mitochondria, MPEP induced a dose-dependent ATP depletion, without affecting mitochondrial functionality. In acellular solutions only MPEP and MTEP reduced ATP content. MPEP addition during I/R significantly reduced LDH, AST and TNF-alpha release respect to ischemic controls.

MPEP, MTEP and Fen protected hepatocytes against ischemic injury. Although an MPEP-dependent ATP depletion occurred in isolated hepatocytes, mitochondria and acellular solutions, mitochondrial functionality was not affected and, in an *ex-vivo* model, MPEP was able to reduce the hepatic I/R injury.

https://doi.org/10.1016/j.dld.2018.01.085

T-08

Establishment of expanding 3D-organoids cultures from human fetal biliary tree stem cells (hBTSCs) as a potential tool for regenerative medicine and disease modeling

S. Safarikia[1], V. Cardinale[2], G. Carpino[3], D. Costantini[1], S. Di Matteo[1], L. Nevi[1], D. Bosco[4], E. Gaudio[5], D. Alvaro[1]

[1] *Department of Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy*
[2] *Department of Medico-Surgical Sciences and Biotechnologies, Polo Pontino, Sapienza University of Rome, Rome, Italy*
[3] *Department of Movement, Human and Health Sciences, Division of Health Sciences, University of Rome "Foro Italico", Rome, Italy*
[4] *Department of Experimental Medicine, Viale Regina Elena 324, Rome 00161, Italy*
[5] *Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Sapienza University of Rome, Rome, Italy*

Recently, 3D-organoids, an advanced culture technology, emerged in the field of stem cells and regenerative medicine, resembling embryonic organ development. The aim of our study was to generate 3D-organoid cultures of fetal biliary tree stem cells (hBTSCs) suitable for *in vitro* disease modeling and regenerative medicine of liver and pancreas.

To isolate *EpCAM/LGR5*-enrichedhBTSCs, fetal biliary tree ($N = 6$) was mechanically and enzymatically digested. Cells were embedded in Matrigel and cultured in an expansion organoid medium containing soluble factors typical of stem cell niches (EGF, FGF, Noggin, R-Spondin1) that represent LGR5-ligands and Wnt-agonists. Culture medium was supplemented with Forskolin, a cAMP-activator, and with a TGFβR-inhibitor to induce cell proliferation and arrest of differentiation. We analyzed colony formation efficiency, organoid size and morphology, cell proliferation, and gene expression by RT-qPCR.

85 ± 7 million ($N = 6$) *EpCAM/LGR5* enriched fetal hBTSCs were obtained. The isolated hBTSCs showed a high tendency to generate organoids with high colony formation efficiency (>90%). After 5 days, the organoids were microscopically detected as spherical structures and after 7 days, they reached a macroscopically visible size. Cell proliferation in organoids was significantly higher compared to 2D conditions ($p < 0.05$). Fetal biliary tree organoids were composed of single layered cuboidal epithelium and inner cell masses. RT-qPCR analysis indicated that organoids expressed multipotency stem cell markers (SOX2, NANOG, OCT4), endodermal stem/progenitor cell markers (LGR5, EpCAM, PDX1, SOX17), hepatic, pancreatic and ductal markers (ALB, CYPA3, INS, CFTR, CK19,) and stem/progenitor surface genes (NCAM, CD133, CD44), recapitulating major processes during embryonic development. Specifically, organoids expressed a higher level of LGR5 compared to 2D cultures ($p < 0.05$).

We have demonstrated that organoids expand clonogenically stable *in vitro* for at least two months, maintaining a stable phenotype of multipotent stem cells. This system has potential applications in regenerative medicine of liver and pancreas and in disease modeling.

https://doi.org/10.1016/j.dld.2018.01.086

T-09

Impact of Neuromedin-B receptor variants on iron overload disorders

R. Rametta[1], G. Baselli[2], P. Dongiovanni[1], S. Pelusi[1], M. Meroni[2], A.L. Fracanzani[1,2], S. Fargion[1,2], L. Valenti[1,2]

[1] *Department of Physiopathology and Transplantation, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy*
[2] *University of Milan, Milan, Italy*

A significant proportion of iron overload heritability remains unexplained. By exploiting next generation whole exome sequencing in three cases of hereditary hemochromatosis (HH) not accounted for by known genetic risk loci, we identified rare mutations predicted to alter protein activity in Neuromedin-B receptor (NMBR), suggesting NMBR may be a candidate gene regulating iron metabolism. NMBR gene encodes for a G-protein-coupled receptor involved in the regulation of appetite, the hypothalamus-pituitary axis, cell contraction and proliferation.

NMBR mutations, identified by sanger sequencing, were significantly enriched in 105 unrelated patients with HH as compared to both 100 local controls with normal iron metabolism (18% vs. 5%, $p = 0.0036$) and 1000Genomes Non Finnish European subjects ($p = 0.002$ at burden test).

Consistently, in 204 patients at risk of iron metabolism alterations due to non-alcoholic fatty liver disease, the most common low-frequency p.L390M variant was also independently associated with higher circulating ferritin ($p = 0.008$).

In 58 individuals without HH, who underwent oral iron tolerance test, p.L390M-variant carriers had higher ferritin and increased transferrin saturation following iron challenge ($p < 0.001$). In a subgroup of 20 individuals, the circulating concentration of NMBR ligand, Neuromedin-B (NMB) assessed by ELISA assay, was significantly down-modulated by iron challenge at 8 h, corresponding to the hepcidin release peak, and was decreased in p.L390M-variant carriers and HH individuals in parallel with increased transferrin saturation.

Finally, NMBR and NMB expression is induced by exposure to iron salts in human HepG2 hepatoma cells and murine primary hepatocytes. Furthermore, in mice NMBR was induced by dietary iron overload in the liver, spleen, pancreas, gut and skeletal muscle, while NMB was downregulated in the gut.

In conclusion, NMBR locus may be involved in the regulation of iron metabolism may represent an interesting therapeutic target for iron disorders.

https://doi.org/10.1016/j.dld.2018.01.087

T-10

Durable response in the markers of cholestasis through 36 months of open-label extension with obeticholic acid in Italian patients with primary biliary cholangitis

P. Andreone[1], A. Floreani[2], P. Invernizzi[3], G. Mazzella[1], J. Owens-Grillo[4], E. Smoot Malecha[4], L. MacConell[4]

[1] *Dipartimento di Scienze Mediche e Chirurgiche, Universtiy of Bologna, Bologna, Italy*
[2] *Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy*
[3] *Program for Autoimmune Liver Disease, International Center for Digestive Health, Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy*
[4] *Intercept Pharmaceuticals, Inc., San Diego, CA, United States*

Obeticholic acid (OCA) is a potent and selective farnesoid X receptor (FXR) agonist indicated for the treatment of primary biliary cholangitis (PBC). This analysis evaluated the long-term efficacy and safety of OCA in Italian patients with PBC.

POISE was a Phase 3, 12-month, double-blind, placebo-controlled study followed by an ongoing open-label extension (OLE). Patients with an alkaline phosphatase (ALP) >1.67× ULN or total bilirubin >ULN to <2× ULN, on a stable ursodeoxycholic acid (UDCA) dose or unable to tolerate UDCA, were randomized to daily Placebo, OCA 5–10 mg, or OCA 10 mg. Data are mean ± SD.

Thirty-two of 216 patients were treated at Italian sites with 29 patients enrolling in the OLE (Placebo, $n = 10$; OCA 5–10 mg, $n = 11$; OCA 10 mg, $n = 8$). In Italian patients, both OCA groups demonstrated significant reductions in ALP (U/L) after 12 months of double-blind treatment (Placebo: 43 ± 108; OCA 5–10 mg: -114 ± 86, $p < 0.01$; OCA 10 mg: -132 ± 104, $p < 0.01$). This response was durable through an additional 36 months of treatment during the OLE (Placebo: -96 ± 96, $p < 0.05$; OCA 5–10 mg: -125 ± 96, $p < 0.01$; OCA 10 mg: -129 ± 121, $p < 0.05$). After 12 months of double-blind treatment, total bilirubin (μmol/L) increased in the Placebo group (2.1 ± 2.5), but remained stable in OCA 5–10 mg and OCA 10 mg groups (-0.6 ± 3.5, $p < 0.05$ and -1.1 ± 1.9, $p < 0.05$). The change from Baseline in total bilirubin at Month 36 of the OLE remained relatively stable with a slight increase in Placebo (Placebo: 1.8 ± 5.6; OCA 5–10 mg: -0.8 ± 3.4; OCA 10 mg: -0.5 ± 4.2). Five (45%) of the Placebo patients in the double-blind phase and 8 (80%) of the Placebo patients initiating OCA in the OLE experienced pruritus.

OCA given to Italian patients resulted in significant improvements in markers of cholestasis and hepatic damage. A durable response was evident throughout the OLE demonstrating the safety and efficacy of long-term OCA treatment.

https://doi.org/10.1016/j.dld.2018.01.088

T-11

A worldwide cross-ethnic study of quality of life in patients with PBC: Attitude or latitude?

M. Carbone[1], L. Montali[2], A. Gragnano[2], M. Miglioretti[2], A. Frigerio[2], M. Yagi[3], F. Malinverno[1], F. Bernuzzi[1], L. Jopson[6], A. Reig[4], S. Pilar[4], A. Pares[4], A. Tanaka[3], G.F. Mells[5], D.E. Jones[6], P. Invernizzi[1], the Japanese PBC Study Group the UK-PBC Study Group ,

[1] *Division of Gastroenterology and Hepatology, Department of Medicine and Surgery, University of Milan Bicocca, Milan, Italy*
[2] *Division of Psychology, University of Milan Bicocca, Milan, Italy*
[3] *Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan & the Japanese PBC*
[4] *Liver Unit, Hospital Clínic, University of Barcelona, Barcelona, Spain*
[5] *Academic Department of Medical Genetics, University of Cambridge, Cambridge, UK*
[6] *Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK*

Background: Several symptoms impairs the quality of life (QoL) of patients with PBC. Fatigue is the symptom with the greatest impact on QoL, particularly when associated with cognitive impairment and emotional dysfunctions. Some studies conducted at a national level pointed out geographical and cultural variations in symptom relevance and impact. The aim of our study was to use national patient cohorts recruited from countries at different latitude/longitude to explore differences of the impact of the disease on perceived QoL.

Methods: We performed a cross-sectional study of PBC patients recruited from four different geographic areas, namely UK, Spain, Italy and Japan. Disease-specific and validated symptom assessment tools (PBC-27) was used. Laboratory investigation was also collected. To validate the factorial structure of the PBC-27 we performed confirmatory factor analyses for every country.

Results: 569 patients participated to the study (90.5% females, mean age 61 years). The PBC 27 scale showed cross-cultural validity. The mean of the *fatigue* domain of the British patients was significantly greater than that of the Japanese ($p < 0.05$), Italian ($p < 0.05$), and Spanish patients ($p < 0.001$). The mean of the *cognitive* domain after 54 years of age, was significantly greater in the British patients than in the Japanese ($p < 0.05$) and Spanish patients ($p < 0.01$). However, after 69 years of age, there were not significant differences between Countries. The mean of the *emotion* domain after 54 years of age, was greater in the British that in the Spanish ($p < 0.01$) and Italian patients ($p < 0.01$).

Conclusions: We showed differences in the four countries concerning fatigue, cognitive and emotional dysfunction. British patients were the most symptomatic with fatigue that scored the highest. The association of latitude and symptoms might provide new insights into the role of vitamin D level, genetics and/or cultural component into disease phenotype in PBC.

https://doi.org/10.1016/j.dld.2018.01.089

T-12

HBV reservoir and enhanced cccDNA transcriptional activity in HBeAg negative chronic hepatitis B

L. Colagrossi[1], R. Salpini[1], U.S. Gill[2], A. Battisti[1], L. Piermatteo[1], D. Di Carlo[1], N. Hansi[2], F. Ceccherini-Silberstein[1], C.F. Perno[3], P.T.F. Kennedy[2], V. Svicher[1]

[1] *University of Rome Tor Vergata, Department of Experimental Medicine and Surgery Via Montpellier, Italy*
[2] *Hepatology, Centre for Immunobiology, Blizard Institute, Barts and The London SMD, QMUL, London, United Kingdom*
[3] *University of Milan "La Statale", Milan, Italy*

Introduction/aim: The basal core promoter (BCP) mutations 1766T, 1764A+1762T cause HBeAg-negativity. However, their impact on modulating the burden and productivity of intrahepatic HBV-reservoir in vivo is controversial.

Methods: This study includes 72 drug-naïve HBeAg-negative chronically-infected patients (D: 45.8%-C: 19.4%-E: 18.1%-A: 9.7%-B: 7%), with a BCP-sequence from liver-biopsy. Intrahepatic cccDNA and pregenomic-RNA (pgRNA) are assessed by qPCR. Serum HBcrAg is measured by Lumipulse (Fujirebio). BCP-mutations are defined according to the reference-sequence of each specific genotype. Mann–Whitney test is used to compare levels of intrahepatic and serum parameters in presence of each BCP mutation and in its absence (referred as wt). BCP binding-affinity for transcription-factors (TF) is estimated by AIggen-algorithm (a decreased dissimilarity-score [DS] indicates an increased binding-affinity in presence of a mutation).

Results: 1766T and 1764A+1762T (occurring in 9.7% and 29.2% of pts) are the only BCP mutations tightly correlated with increased cccDNA (median[IQR]: 2.6[2.2–3.2] and 2.0[1.0–2.5] vs 1.8[0.9–2.2]logcps/1000cells for wt, $P=0.001$ and 0.01) and serum HBV-DNA (median[IQR]: 4.9[3.8–5.4] and 5.0[4.7–5.4] vs 3.4[2.2–4.5]IU/ml for wt, $P=0.003$ and 0.001). Multivariable-analysis confirms that the presence of >1 of these mutations correlates with higher cccDNA and serum HBV-DNA after correcting for patients' demographics, HBV-genotypes, virological parameters (OR[95%CI]: 2.9[1–8.2], $P=0.05$ and 3.3[1.1–9.7], $P=0.03$). 1766T and 1764A+1762T also determine a higher pgRNA (median[IQR]: 20[13–32] and 460[5–1077] vs 2[1–10] cps/1000 cells for wt, $P=0.02$ and 0.006) and HBcrAg (median[IQR]: 4.3[3–5.1] and 4.0[3–4.9] vs 2.6[2–3.3] logU/ml for wt, $P=0.03$ and 0.002), supporting their contribution to an enlarged and more productive HBV-reservoir. Moreover, 1762T+1764A increases binding-affinity for HNF-1alfa TF (DS: 1.8 vs 4.6 for wt) and introduces TF binding site HNF-1beta (absent in wt). Finally, all patients with 1766T present a Ishak-score ≥ 2 ($P=0.001$), suggesting its role in liver-damage.

Conclusions: 1766T and 1764A+1762T tightly correlate with an enriched intrahepatic HBV-reservoir with enhanced productivity. These mutations could help identifying patients at risk of disease-progression and should be considered in therapeutic strategies aimed at silencing cccDNA.

https://doi.org/10.1016/j.dld.2018.01.090

T-13

Genetic profiling using plasma-derived cell-free DNA in therapy-naïve hepatocellular carcinoma patients: A pilot study

G.G. Di Costanzo[1], C.K.Y. Ng[2,3], N. Tosti[3], R. Tortora[1], V. Paradiso[3], M. Coto-Llerena[2], G. Roscigno[4], V. Perrina[3], C. Quintavalle[3], T. Boldanova[3,5], S. Wieland[2], G. Marino-Marsilia[6], M. Lanzafame[3], L. Quagliata[3], G. Condorelli[4], M.S. Matter[3], M.H. Heim[2,5], M. Guarracino[1], L.M. Terracciano[3], S. Piscuoglio[3]

[1] *Department of Transplantation – Liver Unit, Cardarelli Hospital, Naples, Italy*
[2] *Department of Biomedicine, Hepatology Laboratory, University of Basel, Basel, Switzerland*
[3] *Institute of Pathology, University Hospital Basel, Basel, Switzerland*
[4] *Department of Molecular Medicine and Medical Biotechnology, "Federico II" University of Naples, Naples, Italy*
[5] *Division of Gastroenterology and Hepatology, University Hospital Basel, Basel, Switzerland*
[6] *Pathology Unit, Cardarelli Hospital, Naples, Italy*

Background and aim: "Liquid biopsy" has shown clinical potential as a minimally invasive technique for disease monitoring and molecular profiling in cancers. Here we sought to determine if plasma-derived cell-free DNA (cfDNA) captures the genetic alterations of hepatocellularcarcinoma (HCC) in patients who have not undergone systemic therapy.

Materials and methods results: Frozen biopsies from the primary tumor and plasma were synchronously collected from 30 prospectively recruited, systemic treatment-naïve HCC patients. Deep sequencing of the DNA from the biopsies, plasma-derived cfDNA and matched germline was performed using a panel targeting 46 coding and non-coding genes frequently altered in HCCs.

In 26/30 patients, at least one somatic mutation was detected in biopsy and/or cfDNA. Somatic mutations in HCC-associated genes were present in the cfDNA of 63% (19/30) patients and could be reliably detected '*de novo*' without prior knowledge of the mutations present in the biopsy in 27% (8/30) patients. Mutational load and the variant allele fraction of the mutations detected in the cfDNA positively correlated with tumor size and Edmondson grade. Crucially, among the seven patients in whom the largest tumor was $\geq$5 cm or was associated with metastasis, at least one mutation was detected '*de novo*' in the cfDNA of 86% (6/7) cases and the cfDNA captured 99% (94/95) of the mutations found in these patients.

Conclusion: In patients with high disease burden, the use of cfDNA for genetic profiling in lieu of a biopsy maybe feasible. The correlation of detectable somatic mutations and disease burden also points towards the use of cfDNA for disease monitoring in HCC patients. Our results support further investigations into the clinical utility ofcfDNA in a larger cohort of patients.

https://doi.org/10.1016/j.dld.2018.01.091

T-14

Role of rare pathogenic mutations in the development of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease

S. Pelusi[1,2], G. Baselli[1], A. Pietrelli[2,8], P. Dongiovanni[2], M. Meroni[1], B. Donati[1], A.L. Fracanzani[1,2], R. Romagnoli[4], S. Petta[5], L. Miele[6], A. Grieco[6], E. Bugianesi[3], G. Soardo[7], R. De Francesco[8], S. Fargion[1,2], L. Valenti[1,2]

[1] *Department of Pathophysiology and Transplantation, Università Degli Studi Di Milano, Milano, Italy*
[2] *Internal Medicine and Metabolic Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy*
[3] *Division of Gastroenterology, Department of Medical Sciences, A.O.U. Città della Salute e della Scienza, Università di Torino, Torino, Italy*
[4] *Liver Transplant Center, General Surgery 2U, AOU Città della Salute e della Scienza di Torino, University of Torino, Torino, Italy*
[5] *Section of Gastroenterology, Dipartimento Biomedico di Medicina Interna e Specialistica, University of Palermo, Palermo, Italy*
[6] *Institute of Internal Medicine and Gastroenterology Area, Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del S. Cuore, Largo Gemelli, 00168, Rome, Italy*
[7] *Liver Unit, Internal Medicine, Department of Medical Area, University of Udine, Udine, Italy*
[8] *Istituto Nazionale di Genetica Molecolare INGM, Romeo ed Enrica Invernizzi, Bioinformatic group, Milano, Italy*

Introduction: Nonalcoholic fatty liver disease (NAFLD) is recognized as an underlying etiology of hepatocellular carcinoma (HCC). Genetic factors (such as the PNPLA3 I148M variant) play an important role in its pathogenesis.

Aim: We examined by whole exome sequencing (WES) whether pathogenic and rare mutations predicted to alter protein sequence in candidate genes causing inherited liver disease or cancer syndromes are enriched in NAFLD-HCC.

Materials and methods: 72 HCC, 59 cirrhosis patients from Italian tertiary centers and 50 local controls without NAFLD were enrolled. Pathogenic mutations were defined according to ClinVar database, developed to evaluate genotype-phenotype relationships by integrating data from multiple sources, while enrichment in pathogenic variants was validated using public databases (1000 Genomes, $n = 513$).

Results: Already known rare pathogenic mutations in candidate genes were enriched in NAFLD-HCC: 40% of patients reported at least one mutation causing liver disease or cancer predisposition ($p < 0.05$ vs. healthy subjects, $p < 0.005$ vs. 1000G). Among pathogenic mutations, the majority involved genes related to genetic liver disease (42%), cancer predisposition (33%) and lipid metabolism (10%).

In NAFLD-HCC patients we identified a significant enrichment of rare mutations (minor allele frequency < 0.001), resulting in a phenotype predisposing to liver disease (Table 1).

Supporting the pathogenicity of this second group of mutations, carriage of rare APOB mutations was associated with lower circulating triglycerides ($p = 0.001$) and higher HDL cholesterol ($p = 0.008$).

Table 1

Gene	NAFLD-HCC ($n = 72$)	Controls[b] ($n = 563$)	OR	95% c.i.	p value[a]
SQSTM1	3	1	24.0	2.5–234	0.0089
APOB	9	21	3.7	1.6–8.4	0.0104
EGF	2	0	39.9	1.9–840	0.0185
TERF2	3	2	12.2	2.0–74.3	0.0201
TSC2	4	5	6.5	1.7–25.0	0.0238
PNPLA3, 148MM	24	1[c]	24.5	3.2–188	0.002

[a] Evaluated by Burden test.
[b] Local controls and 1000G.
[c] Evaluated only in local controls, $n = 50$.

Conclusions: Rare pathogenic mutations in genes involved in liver disease and cancer predisposition are involved in determining predisposition to NAFLD-HCC.

https://doi.org/10.1016/j.dld.2018.01.092

T-15

Role of the protein tyrosine kinase Mer (MerTK) in the cross-talk between macrophages and hepatic stellate cells

M. Pastore[1], G. Di Maira[1], A. Caligiuri[1], S. Petta[2], F. Marra[1]

[1] *Università di Firenze, Italy*
[2] *Università di Palermo, Italy*

Background and aims: Activation of resident macrophages and recruitment of further inflammatory cells result in activation of hepatic stellate cells (HSCs). MerTK, a receptor tyrosine kinase mainly expressed in macrophages, plays a key role in the initiation of efferocytosis. MerTK is overexpressed in murine models of fibrogenesis and by human HSCs, where mediates profibrogenic actions. In addition, MerTK mutants are associated with higher protein expression are present with higher frequency in patients with NAFLD and significant fibrosis, and macrophages contribute to its expression. This study was undertaken to evaluate the potential effects of MerTK activation in macrophages on HSC phenotype modulation

Method: Primary human HSCs activated on plastic, and the immortalized monocytic line THP1 were employed. THP1 monocytes were differentiated into THP1 macrophages after treatment with phorbol 12-myristate 13-acetate (PMA). Inhibition of MerTK expression or activity was performed by knockdown with siRNA or with the specific inhibitor UNC569. Migration of HSCs was assessed by modified Boyden chamber. HSC viability was measured by MTT assay and gene expression were evaluated by RT-PCR.

Results: Exposure of THP1 cells to PMA resulted in a dramatic upregulation of MerTK expression, at the gene and protein levels. Incubation with Gas-6, a MerTK ligand, caused time-dependent phosphorylation of MerTK on tyrosine residues. Exposure of HSCs to conditioned medium (CM) of differentiated, PMA-treated THP1 cells exposed to Gas-6 induced a significant increase in cell migration and in cell viability compared to control CM. Furthermore, the CM from Gas-6-stimulated THP1cells induced in HSCs an increase in the gene expression of profibrogenic factors compared to control CM. These effects were specifically related to MerTK activity/expression, as indicated by knockdown experiments and by pharmacologic inhibition

Conclusion: These data highlight a novel important role of MerTK in the fibrogenic responses, through a cross-talk between HSCs and inflammatory cells.

https://doi.org/10.1016/j.dld.2018.01.093

T-16

Incomplete normalization of transaminases at 18 months is the most important predictor for failure of biochemical response in autoimmune hepatitis

A. Gerussi[1,2], N. Halliday[3], D. Roccarina[1], F. Saffioti[1,4], P. Polly[1], A. Marshall[1], D. Thorburn[1]

[1] *Sheila Sherlock Liver Centre, Royal Free London NHS Foundation Trust and UCL Institute for Liver and Digestive Health, University College of London, London, United Kingdom*
[2] *Liver Unit, Internal Medicine, Department of Experimental and Clinical Medical Sciences, University of Udine, Udine, Italy*
[3] *Institute of Immunity and Transplantation, UCL, London, United Kingdom*
[4] *Department of Clinical and Experimental Medicine, Division of Clinical and Molecular Hepatology, University of Messina, Messina, Italy*

Autoimmune hepatitis (AIH) can lead to cirrhosis, hepatic failure and death. Lack of response to standard treatment increases the risk of adverse outcomes. We aimed to identify factors that influence achievement of complete biochemical response (CBR) to allow timely identification of patients who require escalation of treatment.

Data were obtained from a retrospective database of all AIH patients attending a single tertiary liver unit since 1980. Patients not meeting IAHG diagnostic criteria for AIH or with other concomitant liver diseases, acute liver failure at onset, less than 18 months follow up, who were never treated, or with incomplete data were excluded. CBR was defined as normalization of aspartate transaminase, alanine aminotransferase and immunoglobulin G levels to within the laboratory normal range.

88 patients were included with a mean age at diagnosis of 43 ± 16 years, 67 (76%) were female. Seventy (79%) achieved complete biochemical response at any time. On univariate analysis, factors significantly associated with failure to ever achieve CBR were black ethnicity, presence of cirrhosis at diagnosis, raised transaminases at 3, 6, 12 and 18 months and non-concordance. Incomplete normalization of transaminases at 18 months was the only independent predictor of failure of CBR on binary logistic regression (OR 0.05, $p < 0.001$). Features at diagnosis associated with incomplete normalization of transaminases at 18 months were younger age, black ethnicity, higher alkaline phosphatase levels (ALP) and cirrhosis. On multivariate analysis all of these factors except cirrhosis independently correlated with incomplete normalization of transaminases at 18 months.

Raised transaminases after 1 year from diagnosis and treatment predict failure to achieve CBR in AIH, therefore further augmentation of treatment should be considered beyond 1 year. Patients at high risk for poor treatment responses include those with young onset, higher ALP and black ethnicity and these patients should have close follow up.

https://doi.org/10.1016/j.dld.2018.01.094

T-17

Characterization of HBV integration landscape in tumor and non-tumor liver tissues by a high-throughput viral integration detection method

D. D'Aliberti[1], D. Giosa[1], G. Raffa[1], C. Musolino[1], G. Tripodi[1], D. Lombardo[1], F. Casuscelli di Tocco[1], C. Saitta[1], O. Romeo[2], G. Navarra[3], G. Raimondo[1], T. Pollicino[3]

[1] *Department of Clinical and Experimental Medicine, Messina, Italy*
[2] *Department of Environmental and Biological Sciences, Messina, Italy*
[3] *Department of Human Pathology, University Hospital of Messina, Messina, Italy*

Introduction: Most data on HBV integration were generated by methods that favor preferential amplification and bias identification of unique integration sites (UISs). The recent next-generation sequencing (NGS) approaches showed a low-coverage of HBV reads.

Aims: To conduct a high-throughput viral integration analysis on tumor (T) and non-tumor (NT) liver tissues, and on PLC/PRF/5 cells, using NGS of enriched HBV integrants; to characterize the HBV DNA integration events; to identify host/HBV junctures at the whole-transcriptome level.

Methods: DNA was fragmented by sonication, blunted, adenosine-tailed and ligated to Linkers. Virus integrations were recovered by PCR using 24 different HBV-primers covering the whole viral genome. Amplicons were subjected to paired-end sequencing on Illumina-MiSeq. RNA-Seq was performed on Illumina-HiSeq-2500. High-quality reads were mapped against hybrid reference including the human genome reference GRCh38.p10 and HBV genome (NC_003977).

Results: We detected 7536 HBV integration breakpoints (5186 in Ts, 2071 in NTs, and 279 in PLC/PRF/5 cells). Among them, 3912 were mapped to UISs (3157 in Ts, 484 in NTs, and 271 in cells), 632 to exons (601 in T, 31 in NT, and 1 in cells), and 1274 to repetitive DNA sequences [LINE (21.4%), SINE (16.4%), and LTR (24%)]. An enrichment of microhomology (MH) sequences between host DNA and HBV integrants was found in most of the chimeras. Clonal expansion of HBV-integrated hepatocytes was more frequent in Ts. Most of the HBV integrants contained preS-S and ENHI/X promoter region sequences. RNA-Seq confirmed the production of viral/human fusion transcripts (HBs-CCDC57 in PLC/PRF/5 cells, HBx-LINE/L1 and HBs-PTPRD in 2 different Ts.)

Conclusion: We developed a high-throughput HBV-integration detection method that allows to characterize thoroughly the landscape of HBV integration events and to identify viral-human chimeric fusion genes that may be involved in HCC development. MH seems to be the main mechanism involved in HBV integration that preferentially occurs into UISs.

https://doi.org/10.1016/j.dld.2018.01.095

T-18

Incidence and outcome of portal vein thrombosis in HCV cirrhotic patients treated with direct-acting antivirals: A single-center prospective 3-year study

E. Degasperi[1], G. Tosetti[1], R. D'Ambrosio[1], A. Aghemo[2], M. Borghi[1], R. Soffredini[1], M. Primignani[1], P. Lampertico[1]

[1] *CRC "A. M. e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[2] *Humanitas University Department of Biomedical Sciences, Rozzano-Milan, Italy*

Background and aim: Treatment of hepatitis C virus (HCV) with direct-acting antivirals (DAAs) improves cirrhosis outcomes, however portal vein thrombosis (PVT) risk is still undefined. We evaluated incidence and predictors of PVT in HCV cirrhotics treated with DAAs.

Methods: HCV CPT A-B cirrhotics without PVT consecutively receiving DAAs between November 2014 and December 2016 at a single center were enrolled. Patients underwent regular blood tests, 6-month abdominal imaging and esophageal varices (EV) screening. PVT was graded according to Yerdel classification.

Results: 557 HCV cirrhotics were enrolled: age was 64 (28–87) years, 60% males, 83% CPT A, platelet count (PLT) was 118 (26–753) $\times 10^3$/mL, spleen size 13 (7–24) cm, LSM 17.0 (12.1–75.0) kPa, 32% had baseline EV. During 22 (1–36) months of follow-up, 9 (1.6%) patients developed PVT, with a 3-year cumulative probability of 2%. PVT patients were CPT B (56%), all had EV at baseline (small varices in 2, primary prophylaxis in 4, secondary in 3). PVT were Yerdel grade 1 in 4 patients, grade 2 in 3, grade 3 and 4 in 1 patient. No PVT was related to tumor vascular invasion. PVT resulted in de novo or worsening of ascites in 4 (44%) patients, while it was asymptomatic in 5 (56%). At PVT diagnosis, EV worsened compared to baseline in 3 (33%) patients but no GI bleeding occurred. Baseline predictors of PVT reflected disease severity (CPT, MELD, bilirubin, albumin) and portal hypertension (EV, PLT). The 3-year cumulative probability of PVT was 5.2% vs 0% in patients with or without baseline EV, respectively ($p = 0.002$). PVT was treated by anticoagulation in 8 patients, leading to partial or complete PVT recanalization in 6 patients after 4 (3–7) months from anticoagulation start.

Conclusions: Among HCV cirrhotics treated with DAA, non neoplastic PVT is a rare complication but may cause clinical decompensation.

https://doi.org/10.1016/j.dld.2018.01.096

T-19

The exposure of primary cultures of human biliary tree stem/progenitor cells (hBTSCs) to different micro-environmental factors induces proliferation, epithelial-mesenchymal transition (EMT) and senescence, which are typical pathological features of human cholangiopathies

D. Costantini[1], V. Cardinale[2], G. Carpino[3], L. Nevi[1], S. Di Matteo[1], S. Safarikia[1], F. Melandro[4], P. Berloco[4], E. Gaudio[5], D. Alvaro[1]

[1] *Department of Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy*
[2] *Department of Medico-Surgical Sciences and Biotechnologies, Polo Pontino, Sapienza University of Rome, Rome, Italy*
[3] *Department of Movement, Human and Health Sciences, Division of Health Sciences, University of Rome "Foro Italico", Rome, Italy*
[4] *Department of General Surgery and Organ Transplantation, Sapienza University of Rome, Rome, Italy*
[5] *Division of Human Anatomy, Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Sapienza University of Rome, Italy*

The stimulation of human biliary tree stem/progenitor cells (hBTSCs) in peribiliary glands (PBGs) have been demonstrated in several cholangiopathies, such as Primary Sclerosing Cholangitis (PSC) and Cholangiocarcinoma (CCA). hBTSCs also display features of EMT, senescence and dysplasia in these pathologies. Our aim was to investigate which effects putative agents of human cholangiopathies reproduce in primary cultures of hBTSCs. hBTSCs were isolated from donor organs ($N = 6$), grown in self-renewal control conditions (Kubota's Medium) and exposed (from 24 h to 10 days) to concentrations of lipopolysaccharides (LPS), oxysterols, hydrophobic biliary salts, or high glucose. Viability (MTS assay), Population Doubling (PD), the expression (RT-qPCR) of pluripotency, transit-amplifying compartment, EMT, pNF-κB and HDAC6 genes and senescence associated secreted phenotype (SASP) by IF and ELISA were investigated. Glycochenodeoxycholate (0.5 mM), LPS (200 ng/ml), oxysterols [(+)-4-Cholesten-3-one (0.14 mM), Cholesta–4,6–dien-3-one (0.14 mM), 5α-Cholestan-3-one (0.14 mM)] or high concentrations of Glucose (28 mM) did not affected viability of hBTSCs. LPS, Cholesta-4,6-dien-3-one and Glucose induced a significant increase of cell proliferation after 10 days of exposure ($p < 0.01$). The MTS assay confirmed a high proliferation rate after chronic exposure to LPS, oxysterols, or high glucose ($p < 0.01$). A significant increase of markers of transit-amplifying compartment and EMT ($p < 0.05$) occurred in presence of Cholesta-4,6-dien-3-one while, LPS and high Glucose effect was an increased expression of PCNA and EMT genes. Increased senescent cells after 10 days of exposure to each of the investigated factor compared to controls ($p < 0.01$) were observed. LPS, Cholesta-4,6-dien-3-one and high Glucose induced enhanced IL-6 secretion compared to controls ($p < 0.01$), high levels of pNF-κB and HDAC6 ($p < 0.01$), and traces of LC3 protein, suggesting inflammation-induced autophagy.

We identified micro-environmental agents inducing in hBTSCs proliferation, enhanced expression of pluripotency and transit-amplifying genes, EMT and senescence, reproducing the pathologic features of PBGs in human cholangiopathies.

https://doi.org/10.1016/j.dld.2018.01.097

T-20

Hepatitis C virus eradication by direct antiviral agents improves carotid atherosclerosis in patients with advanced fibrosis/compensated cirrhosis

S. Petta[1], L.E. Adinolfi[2], A.L. Fracanzani[3], V. Calvaruso[1], F. Rini[1], C. Cammà[1], V. Di Marco[1], A. Marrone[2], R. Nevola[2], A. Pinto[4], L. Rinaldi[2], D. Torres[4], A. Tuttolomondo[4], L. Valenti[3], S. Fargion[3], A. Craxì[1]

[1] *Sezione di Gastroenterologia e Epatologia, Di.Bi.M.I.S, Università di Palermo, Italy*
[2] *Department of Medical, Surgical, Neurological, Geriatric, and Metabolic Sciences, University of Campania "Luigi Vanvitelli", 80100 Naples, Italy*
[3] *Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy*
[4] *Sezione di Medicina Interna con Stroke Care, Dipartimento Biomedico di Medicina Interna e Specialistica (Di.Bi.M.I.S), Università di Palermo, Italy*

Introduction/aim: We aimed to assess whether HCV eradication by direct antiviral agents (DAA)-based therapies improves carotid atherosclerosis in HCV-infected patients with advanced fibrosis/compensated cirrhosis.

Method: 182 consecutive HCV-infected patients with advanced fibrosis/compensated cirrhosis were evaluated. All patients underwent DAA-based antiviral therapy according to AISF/EASL guidelines. Intima-media thickness (IMT) and carotid plaques, defined as focal thickening of $\geq$1.5 mm at the level of common carotid, were evaluated using ultrasonography at baseline and 9–12 months after the end of antiviral therapy.

Results: Fifty-six percent of the population were males, mean age was 63.1 $\pm$ 10.4 years and 65.9% had compensated cirrhosis. One patient in five had diabetes, 14.3% were obese, 41.8% arterial hypertension and 35.2% were smokers. Mean IMT was 0.94 $\pm$ 0.29 mm, 42.9% had IMT $\geq$ 10 mm, and 42.9% had carotid plaques. All patients achieved a sustained virological response (SVR). Baseline factors independently associated with IMT as linear variable, with IMT $\geq$ 10 mm and with carotid plaques was older age ($p < 0.05$ for all variables in all models). IMT significantly reduced from baseline to 9–12 months after SVR (0.94 $\pm$ 0.29 mm vs. 0.81 $\pm$ 0.27, $p < 0.001$). Consistently, a significant reduction in the prevalence of patients with IMT $\geq$ 10 mm from baseline to follow-up was observed (42.8% vs. 17%, $p < 0.001$), while no changes were reported for carotid plaques (42.8% vs. 47.8%, $p = 0.34$). At linear regression analyses no factors were associated with IMT changes from baseline to follow-up ($p > 0.10$ for all). Consistently, a significant reduction in the IMT and in the prevalence of patients with IMT $\geq$ 10 mm from baseline to follow-up was observed in patients older/younger than 65 years, obese/nonobese, smokers/no smokers, with/without diabetes and with/without arterial hypertension ($p < 0.05$ for all).

Conclusion: HCV eradication by DAA improves carotid atherosclerosis in patients with advanced fibrosis/compensated cirrhosis with/without metabolic risk factors. Data about the impact of HCV eradication in patients with mild liver disease must be explored.

https://doi.org/10.1016/j.dld.2018.01.098

T-21

Health-economic evaluation of different organizational models to manage the Hepatitis C patient journey

S. Fagiuoli[1], L. Pasulo[1], F. Maggiolo[2], R. Spinella[3], P. Del Poggio[3], R. Boldizzoni[4], M. Di Marco[5], A. Aronica[6], C. Benedetti[6], P. Correale[6], C. Garavaglia[6], C. Nicora[7]

[1] *U.O.C. Gastroenterologia – Epatologia e Trapiantologia – ASST Papa Giovanni XXIII – Bergamo, Italy*
[2] *U.O.C. Malattie Infettive – ASST Papa Giovanni XXII, Bergamo, Italy*
[3] *Medicina Istituti Ospedalieri Bergamaschi – (Bg), Italy*
[4] *U.O.C. Medicina ASST Bergamo Ovest – Treviglio (Bg), Italy*
[5] *U.O.C. Medicina A.S.S.T. Bergamo Est – Ospedale "Bolognini", Seriate (Bg), Italy*
[6] *Tefen Management Consulting, Milano, Italy*
[7] *Direzione Generale – ASST Papa Giovanni XXIII, Bergamo, Italy*

Introduction and aims: Directly-Acting-Antivirals (DAAs) transformed HepatitisC treatment. Access to DAAs in Italy was initially constrained to more severe patients. As of mid-2017, the Italian-Medicines-Agency expanded access to DAAs to all HCV-patients, to achieve the elimination by 2030, so the treatment capacity of the healthcare-system is pivotal. The study objective is to investigate different hospitals' organizational-models in terms of their treatment capacity.

Methods: The study compares two models: Centralized Model (CM), where only few Centres of Excellence (CoE) in a region prescribe and deliver DAAs, and Hub&Spoke (H&S) model, where the Hub (CoE) prescribes and delivers DAAs, while Spokes (smaller hospitals) can only prescribe them. Patient journey and workloads were mapped and quantified through interviews with hospital stakeholders. Healthcare cost data were collected through the hospital's IT-system; the sample comprised 2278 HCV-mono-infected patients, treated or deferred over one year (June 2015–June 2016). The comparison of the two models highlighted how to optimize the patient journey while managing a larger number of HCV-patients.

Results: The average costs to treat HCV-patients are comparable between H&S and CM (€1479 vs €1470 per-patient). Key cost drivers are lab-tests (60%), 75% of which related to devices, and specialist visits (30%). Over one year, the H&S model is able to treat 68% more patients than the CM. As it was observed that deferred patients absorb up to 40% of total healthcare costs, two key improvements have been identified to optimize the H&S, creating "optimized H&S model": reduction of the number of specialists' visits, during diagnosis and treatment, due to less severe patients being on waiting lists; involvement of General-Practitioners during follow-up of treated patients without comorbidities/side-effects. These two organizational levers accelerate depletion in waiting-lists and reduce management costs of the deferred patients by 72%vs the CM.

Conclusion: The study demonstrates the importance of a hospital's organizational model in achieving 2030 HCV elimination as efficiently as possible.

https://doi.org/10.1016/j.dld.2018.01.099

T-22

Effectiveness and safety of DAA treatment for recurrent hepatitis C after liver transplantation: The NAVIGATOR Lombardia-Veneto network

F. Invernizzi[1], L. Pasulo[2], A. Aghemo[3], M. Puoti[4], S. Zaltron[5], F. Maggiolo[6], G. Rizzardini[7], S. Fargion[8], P. Sacchi[9], R. Gulminetti[9], M. Zuin[10], T. Quirino[11], M.G. Rumi[12], A. Pan[13], P. Grossi[14], A. Rossini[15], A. Corbellini[16], C. Uberti Foppa[17], L. Belli[18], S. Piovesan[19], P. Angeli[20], L. Chemello[20], F.P. Russo[21], P. Burra[21], V. Vincenzi[22], A.M. Cattelan[23], G. Carolo[24], F. Capra[24], G. Carlotto[25], P.A. Rovere[26], S. Lobello[27], P. Scotton[28], S. Panese[29], P. Fabris[30], A. Alberti[19], P. Lampertico[1], S. Fagiuoli[2], on behalf of the NAVIGATOR study group

[1] *CRC "A. M. e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[2] *Gastroenterology, ASST Papa Giovanni XXIII, Italy*
[3] *Humanitas University, Department of Biomedical Sciences, Rozzano-Milan, Italy*
[4] *Infectious Diseases ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[5] *Infectious Diseases, Spedali Civili, Brescia Bergamo, Italy*
[6] *Infectious Diseases, ASST Papa Giovanni XXIII, Bergamo, Italy*
[7] *Infectious Diseases, Sacco Hospital, Italy*
[8] *Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[9] *Infectious Diseases, Policlinico Pavia, Italy*
[10] *Gastroenterology, San Paolo Hospital, Milan, Italy*
[11] *Infectious Diseases, Busto Arsizio Hospital, Varese, Italy*
[12] *Hepatology, San Giuseppe Hospital, Milan, Italy*
[13] *Infectious Diseases Cremona Hospital, Italy*
[14] *Infectious Diseases Varese Hospital, Italy*
[15] *Hepatology, Spedali Civili, Brescia Bergamo, Italy*
[16] *Infectious Diseases Vizzolo Predabissi Hospital, Italy*
[17] *Immunology and Infectious Diseases, San Raffaele Hospital, Milan, Italy*
[18] *Hepatology Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[19] *DMM, University of Padova, Padova, Italy*
[20] *Clinica Medica 5, University of Padova, Padova, Italy*
[21] *Dipartimento di Scienze Chirurgiche, Oncologiche e Gastroenterologiche (DiSCOG), University of Padova, Padova, Italy*
[22] *Ospedale Belluno, Belluno, Italy*
[23] *Azienda Ospedaliera di Padova, Padova, Italy*
[24] *University of Verona, Verona, Italy*
[25] *Ospedale Santorso, Vicenza, Italy*
[26] *Ospedale Legnago, Verona, Italy*
[27] *Ospedale S Antonio-Padova, Padova, Italy*
[28] *Ospedale Treviso, Treviso, Italy*
[29] *Ospedale Venezia Mestre, Venezia, Italy*
[30] *Ospedale Vicenza, Vicenza, Italy*

Background/aim: Hepatitis C virus (HCV) recurrence after liver transplantation (LT) is universal and introduction of direct-acting antiviral agents (DAAs) has dramatically increased possibility of curative treatment. This study was aimed to report the rate of virological response to DAA treated recipients with recurrent HCV after LT.

Materials/methods: This is a multicentre cohort study performed in 18 Lombard and 11 Venetian centers. From December 2014 to October 2017, all consecutive LT patients with recurrent HCV treated with DAA were enrolled. Data were collected via electronic web based CRF.

Results: 518 HCV-RNA + LT patients received DAA-treatment (with/without IFN) after a median time of 47 months (1–361) after LT. At DAA-starting age was 61 years (30–84), 79% males, 66% HCV-1 infected (1b prevalent), 16% with compensated cirrhosis while 10% with decompensated disease (CPT-score > 6), HCV-RNA level was 1.696.377 UI/mL (50–68,605,835). A SOF-based regimen was administered to 489 patients (94%): 68 SOF + RBV, 262 SOF + LDV ± RBV, 43 SOF + SMV ± RBV, 109 SOF + DCV ± RBV, 7 SOF + Velpatasvir ± RBV. Treatment duration was 12 weeks (2–48). Therapy was well tolerated: only 9% of patients reported sides effects (mostly anaemia and asthenia). Median eGFR (by Cockcroft-Gault formula) did not changed from baseline to and-of-treatment and week 24 post-therapy (72 vs 73 vs 76 ml/min).

Among 383 patients with available SVR data, 367 (96%) achieved a sustained virological response. Sixteen patients showed virological relapse; all of them (except one) were male age 61 yrs (49-70), 7 GT-1b, 5 GT-1a, 2 GT-3 and 2 GT-4, median HCVRNA level 1,955,100 UI/mL (68–65,200,000), 3 compensated cirrhotics and 1 decompensated, 5 received SOF + RBV, 4 SOF + LDV + RBV, 7 SOF + SMV + RBV; in one case virological relapse occurred very late (week 24 post-treatment). After a follow-up of 24 months (2–35), 3% of patients died.

Conclusions: SOF-based therapy for 12-24 weeks is highly effective and safe for the treatment of post-LT recurrent HCV in a real-life multi-center experience.

https://doi.org/10.1016/j.dld.2018.01.100

T-23

IL28 polymorphism and HCC after DAAs for chronic hepatitis C

A. Simili, G. Mazzella, F. Ravaioli, F. Davide, M.L. Bacchi-Reggiani, A. Porro, F. Bazzoli, F. Azzaroli

Department of Medical and Surgical Sciences, University of Bologna, Section of Gastroenterology, S. Orsola-Malpighi Hospital, Bologna, Italy

Background and aim: Eradication of HCV infection reduces the risk of developing hepatocellular carcinoma (HCC). However, cirrhotics remains at risk of developing HCC even after sustained virological response (SVR). Our aim was to evaluate whether the IL28 (rs 12979860) single nucleotide polymorphisms (SNP) may constitute a predisposing genetic factor and improve the identification of SVR patients who remain at risk of developing HCC.

Material: Two hundred patients undergoing DAAs treatment of chronic hepatitis C with advanced fibrosis (F3-F4) were consecutively enrolled. All patients underwent a single blood draw after SVR24 was reached. Beside normal routine laboratory testing for HCV, patient's sera were evaluated also for retinol and retinol binding protein 4 and the following SNPs: PNPLA3 (rs 738409), TM6SF2 (rs 58542926), MBOAT7 (rs 641738), IL28B (rs 12979860), TIMP-1 (rs 4898), TIMP-2 (rs 8179090), NF-kB promoter (rs 28362491). Statistical analyses were conducted using Stata statistical software (Stata Corp, College Station, TX).

Results: Almost all patients (197/200) obtained an SVR at 24 months. Overall, 22 patients (17 M/5F) developed HCC of whom 17 before treatment and 5 after therapy. Of the 17 patients treated for HCC before antiviral therapy (10 surgery, 9 TACE/PEI, 4 RFA), 6 (previous treatment: 4 surgery, 1 PEI, 1 RFA) developed a recurrence after a mean period of 18 months. All patients who developed an HCC obtained an SVR24. A significant association between the variables under study and HCC development was observed only for IL28B–TT genotype in males (10 out of 17; OR 4.862, CI 95% 1.202–19.668, $p = 0.027$).

Conclusion: IL28B rs12979860 polymorphism was significantly associated with HCC development after SVR obtained with DAAs suggesting that determination of this SNP is advisable to better identify patients at risk of tumor development after treatment. Prospective studies are needed to confirm these hypotheses.

https://doi.org/10.1016/j.dld.2018.01.101

T-24

Non-invasive measurement of HVPG using graph analysis based on dynamic contrast-enhanced ultrasound with ESAOTE MyLab: The CLEVER Study

F. Piscaglia[1], A. Berzigotti[2,3], I. Amat-Roldan[4], V. Sansone[1], H. Stefanescu[1,5], B. Procopet[3,5], I. Bilbao-Areste[4], G. Allegretti[1], S. Lens[3], J.-C. Garcia-Pagan[3], C. Di Bonaventura[1], F. Ravaioli[1], L. Mulazzani[1], R. Golfieri[6], R. Vukotic[1], J. Bosch[3], on behalf of the CLEVER Study investigators

[1] *Department of Medical and Surgical Sciences, University of Bologna, Italy*
[2] *Hepatology, Inselspital, University of Bern, Switzerland*
[3] *Liver Unit, Hospital Clínic-IDIBAPS, University of Barcelona, Spain*
[4] *Ymaging, Barcelona, Spain*
[5] *Hepatology Unit, Regional Institute of Gastroenterology and Hepatology, Cluj Napoca, Romania*
[6] *Radiology Unit, General and University Hospital S. Orsola-Malpighi, Bologna, Italy*

Background and aims: Non-invasive methods accurately estimating hepatic venous pressure gradient (HVPG) are un unmet clinical need. Preliminary data suggested that graph analysis of dynamic contrast enhanced ultrasonography (DCE-US) of the liver using a "connectome" approach allows assessment of the liver microcirculatory derangement and mirrors the severity of portal hypertension (Amat-Roldan et al. Radiology 2015). The EC-funded prospective CLEVER study (FP7-IAPP-GA-2013-612273-CLEVER) is aimed at developing a novel automatized software based on DCE-US able to improve prognostication in cirrhosis. First extended results were developed with a Siemens Acuson Sequoia in Barcelona, showing optimal correlation with HVPG. Here we report the adaptation of this CLEVER software to DCE-US videos acquired with ESAOTE MyLab equipments in Bologna to predict HVPG in a population of patients with F≥3 hepatopathy.

Method: Ten seconds long videoclip(s) of the right liver lobe were recorded in each patient producing one cycle of microbubble disruption and reperfusion during SonoVue infusion. A total of 90 videos from randomly selected 47 patients were utilized to optimize the autoselection algorithm of the computer among 5 models based on platelet count and spleen diameter.

Results: Applicability: the CLEVER software was technically able to provide portal pressure estimations from DCE-US in 41/90 videos corresponding to 28/47 patients (59.6%). The Spearman coefficient of correlation between CLEVER values and HVPG was $r = 0.585$ ($p < 0.001$). The CLEVER software was then tested in a separate validation set of 17 technically successful patients, showing a correlation $r = 0.701$ ($p < 0.002$).

Conclusion: We developed and validated the DCE-US based CLEVER software which allows an automatic and quantitative non-invasive estimation of portal pressure in patients with CLD. Larger set of patients with precise subgrouping will help improving the non-invasive predictability of portal pressure by DCE-US.

https://doi.org/10.1016/j.dld.2018.01.102

T-25

A spleen stiffness measurement-based model for the recognition of high risk varices: Baveno VI criteria and beyond

A. Colecchia[1,5], F. Ravaioli[1], G. Marasco[1], A. Colli[6], E. Dajti[1], A. Di Biase[3], M.L. Bacchi Reggiani[2], A. Berzigotti[4], M. Pinzani[7], D. Festi[1]

[1] *Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy*
[2] *Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Italy*
[3] *Department of Pediatrics, University of Modena, Modena, Italy*
[4] *Hepatology, Inselspital, University Clinic of Visceral Surgery and Medicine (UVCM), University of Bern, Switzerland*
[5] *UOC, Gastroenterologia, Azienda Ospedaliera Universitaria Integrata, Verona, Italy*
[6] *Department of Internal Medicine, General Hospital, Lecco, Italy*
[7] *Department of Hepatology, Royal Free Hospital NHS Trust; Institute for Liver and Digestive Health, University College London, London, Great Britain, UK*

Introduction: Recently, Baveno VI guidelines suggested that esophagogastroduodenoscopy (EGD) can be avoided in patients with cACLD who have a liver stiffness measurement (LSM) < 20 kPa and platelet count >150,000/mm^3.

Aims: We aimed to assess the performance of spleen stiffness measurement (SSM) in ruling out patients with high risk varices (HRV), validate Baveno VI criteria (BaVI) and assess how the sequential use of BaVI and SSM could safely avoid the need for endoscopy.

Material and method: We retrospectively analysed 498 cACLD patients who had undergone LSM/SSM by transient elastography (TE), platelet count and EGDs from 2012 to 2016 referred to our tertiary centre. The derivation dataset consisted of 54 randomly selected cases and 129 randomly selected controls from the original datasets of 100 cases and 398 controls; consequently, the validation dataset includes 46 cases and 123 controls.

Results: At the multivariate analysis, SSM, LSM, platelet and Child-Pugh B were independent predictors of HRV. SSM cut-off ≤ 46 kPa was chosen to rule out patients with HRV. The performance of SSM in ruling out HRV showed a sensitivity of 97.8%, a specificity of 44.9%, NPV of 98.9% and an LR- of 0.05. Applying the newly identified SSM cut-off or BaVI, 36.7% and 21.7% of patients could have avoided EGD, with HRV being missed in 1% in both cases. The combination of SSM with BaVI would have made it possible to avoid an

additional 22.5% of EGDs if compared with BaVI alone, thus reaching a final value of 44.2% of avoided EGD, with <5% missed HRV.

Conclusion: SSM is an independent predictor of the presence of HRV, also an accurate and non-invasive test for ruling out HRV and that combining it with BaVI in a simple sequential algorithm makes it possible to safely avoid a significant larger proportion of unnecessary endoscopies.

https://doi.org/10.1016/j.dld.2018.01.103

T-26

Natural killer cell trafficking dysfunction in hepatocellular carcinoma

G. Missale[1], C. Carone[2], D. Canetti[1], V. Regina[1], V. Capizzuto[1], A. Olivani[1], R. Dalla Valle[3], C. Ferrari[1], E. Cariani[2]

[1] *Infectious Diseases and Hepatology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy*
[2] *Toxicology and Advanced Diagnostics, Ospedale S. Agostino-Estense, Modena, Italy*
[3] *Department of Surgery, University of Parma, Parma, Italy*

Introduction: Natural Killer (NK) cells represent one of the most important arms of anti-tumor immune activity. Reduced intra-tumor NK cell infiltrate and dysfunction have been observed in several human solid tumors, including hepatocarcinoma (HCC), and associated with poor clinical outcome.

Aim: To investigate the molecular mechanisms associated with NK cell functional deficiency in HCC.

Materials and methods: Tumor and non-tumorous tissues obtained from 11 patients undergoing liver resection for early HCC in HCV-related cirrhosis were processed in order to derive viable lymphomononuclear cell infiltrate. CD56+CD3− NK cells were derived by fluorescence flow-cytometry cell sorting. Genomic expression on tissue infiltrating NK cells was studied by RNA extraction, PCR amplification followed by hybridization with Sure Print G3 Human GE v3 60K (Agilent). Microarrays data were analyzed by Ingenuity Pathway Analysis 8.5 (IPA) software.

Results: Comparison of non-tumor liver infiltrating NK-cells (L-NK) and tumor infiltrating NK-cells (T-NK) showed 22 differentially expressed (DE) genes (10 up and 12 downregulated). Functional analysis showed activation of a single pathway, Phospholipase C Signaling, in L-NK. Analysis based on function and networking of DE genes showed activation of functions: “cell movement of leukocytes” and “transmigration of mononuclear leukocytes”, both upregulated in L-NK vs T-NK. Next we analyzed networks in order to identify biologically relevant (hub) genes. The hub gene of the L-NK/T-NK network was CCR2, involved in NK cell recruitment during inflammation that was downregulated in T-NK cells.

Conclusion: Our results suggest impaired activation of NK cells in HCC and identify cell movement, adhesion and migration as possible mechanisms involved in NK-cell dysfunction.

https://doi.org/10.1016/j.dld.2018.01.104

T-27

SVR is the strongest predictor of occurrence and recurrence of hepatocellular carcinoma in HCV cirrhotic patients after treatment with direct acting antivirals: A prospective multicenter Italian study

A. Lleo[1], A. Aglitti[2], A. Ciancio[3], V. Di Marco[4], A. Aghemo[1], P. Lampertico[5], M.R. Brunetto[6], M. Zuin[7], P. Andreone[8], E. Villa[9], G. Troshina[3], V. Calvaruso[4], E. Degasperi[5], B. Coco[6], A.M. Giorgini[7], F. Conti[8], A. Di Leo[10], L. Marzi[9], V. Boccaccio[1], S. Bollani[10], P. Maisonneuve[11], M. Rendina[12], M. Persico[2], S. Bruno[1]

[1] *Internal Medicine and Hepatology, Humanitas University, Milano, Italy*
[2] *Internal Medicine and Hepatology Unit, University of Salerno, Naples, Italy*
[3] *Gastroenterology, University of Torino, Torino, Italy*
[4] *Gastroenterology, University of Palermo, Palermo, Italy*
[5] *Gastroenterology and Hepatology, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico di Milano, Milano, Italy*
[6] *Hepatology, University Hospital of Pisa, Pisa, Italy*
[7] *Internal Medicine, San Paolo Hospital, Milano, Milano, Italy*
[8] *Scienze Mediche e Chirurgiche, University of Bologna, Bologna, Italy*
[9] *University of Modena and Reggio Emilia, Modena, Italy*
[10] *Ospedale Fatebenefratelli e Oftalmico, Milano, Italy*
[11] *Division of Epidemiology and Biostatistics, European Institute of Oncology, Milano, Italy*
[12] *Gastroenterology and Digestive Endoscopy, University of Bari, Bari, Italy*

Patients with hepatitis C virus (HCV) related cirrhosis have an expected high rate of progression to liver decompensation and hepatocellular carcinoma (HCC); dramatic improvement in viral eradication rates has been reached with direct antiviral agents (DAAs). Nevertheless, the real benefit of viral eradication after DAAs on disease progression, including HCC development, are still limited and controversial. We aim to prospectively assess the risk of HCC occurrence and early recurrence in a large prospective cohort of DAA-treated HCV-cirrhotic patients.

We analysed data prospectively collected from HCV-infected cirrhotic patients consecutively treated with DAA from January to December 2015 in 10 tertiary liver centers in Italy. Patients with either compensated or decompensated cirrhosis and/or previous HCC were enrolled and followed for 1 year after SVR12. 1927 patients were included; 161 patients had a previous history of HCC. 1832 patients (95%) achieved SVR. Of the 161 patients with past HCC, 38 developed tumor recurrence during the follow-up (incidence person-year 24.8%). Patients with SVR had a significantly lower rate of HCC recurrence. Cox regression analysis highlighted SVR (HR 8.43; $p = 0.0001$) and alfafetoprotein (HR 6.50; $p = 0.002$). Both SVR and alfafetoprotein were confirmed as solid predictors of recurrence at the multivariate analysis. 50/1766 patients (2.8%) without a previous HCC history developed HCC during the follow-up (cumulative incidence p-year, 2.4%). Patients with SVR had a significantly lower rate of HCC recurrence at all time points. SVR was confirmed as the strongest predictor of HCC incidence from the multivariate analysis (HR 5.02; 95% CI: 2.34–10.8; $p < 0.0001$).

This large real-life study highlights that SVR is associated with a significant decrease of recurrent or de novo HCC in cirrhotic patients treated with DAA. Longer follow up is underway to confirm these findings.

https://doi.org/10.1016/j.dld.2018.01.105

T-28

Assessing the risk of *de novo* neoplasms after liver transplantation: Role of pre-transplant hepatocellular carcinoma

S. Shalaby[1], M. Taborelli[2], A. Zanetto[1], A. Ferrarese[1], C. Becchetti[1], S.S. Sciarrone[1], M. Gambato[1], G. Germani[1], M. Senzolo[1], F.P. Russo[1], G. Zanus[3], U. Cillo[3], P. Piselli[4], D. Serraino[2], P. Burra[1]

[1] *Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy*
[2] *Cancer Unit, CRO National Cancer Institute, IRCCS, Aviano, Italy*
[3] *Hepatobiliary Surgery and Liver Transplantation Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy*
[4] *Department of Epidemiology, National Institute for Infectious Diseases L. Spallanzani, Rome, Italy*

Introduction: Patients with hepatocellular carcinoma (HCC) are at higher risk for second-primary malignancies compared with general-population; such risk could be even higher after liver-transplantation (LT). Patients transplanted for alcoholic-cirrhosis or primary sclerosing-cholangitis have been demonstrated to be at higher risk for post-LT *de-novo* neoplasms (DNN). However, evidence on the additional risk that pre-LT HCC could confer are lacking. As HCC has become the leading LT indication, it is important to investigate whether such patients deserve more intensive post-LT DNN-screening.

Materials and methods: A cohort study was conducted among 9 Italian-centers between 1985 and 2014, excluding: ≤18 years old, follow-up shorter than 30 days, cancer-diagnosis within 30 days after LT. Person-years (PYs) at risk for DNN were computed from 30 days post-LT to death, cancer-diagnosis or end of follow-up. Hazard-ratios (HR) of DNN-development (excluding non-melanoma skin cancers) and 95%-confidence intervals (CI 95%) were estimated for HCC-transplanted patients compared to those without pre-transplant neoplastic-history. All models were adjusted for sex, age and calendar year at transplant.

Results: A total of 2757 patients were followed-up for 18,021-PYs during which 194(7%) developed 207 DNN. Out of 980 HCC-patients 65(6.6%) developed 67 DNN, while out of 1777 non-HCC patients 129(7.3%) developed 140 DNN. No significant association with risk of all DNN emerged for HCC-patients compared to non-HCC (HR = 1.18, CI95%: 0.85–1.64), after median follow-ups of 3.8 (IQR: 2.0–6.9) and 6.5 years (IQR: 2.9–11.3), respectively ($p < 0.01$). Median time from LT to DNN-diagnosis was 2.5 years (IQR: 1.5–4.3) for HCC-patients and 4.3years (IQR: 1.8–7.9) for non-HCC ($p < 0.01$). Analyzing specific tumor-types, significant increased-risk emerged for bladder-cancer only (HR = 9.16, CI 95%: 1.1–77).

Conclusions: In our cohort, HCC-transplanted patients were not at higher risk for DNN than other transplanted-patients. Nonetheless, DNN seemed to occur earlier in HCC-patients, probably due to higher carcinogens-susceptibility and shared risk-factors with primary-cancer, leading to an accelerated carcinogenic-process. Pre-LT liver neoplastic-history could represent an additional risk-factor for early-DNN occurrence and should be taken into account for surveillance-individualization.

https://doi.org/10.1016/j.dld.2018.01.106

T-29

Shear wave elastography to assess spleen stiffness: Its feasibility and reproducibility in patients with chronic liver disease and its utility in the prediction of portal hypertension

C.B. Conti[1], M. Giunta[1], G. Casazza[2], D. Gridavilla[1], V. La Mura[1], G. Tosetti[1], A. Nicolini[3], M. Primignani[1], D. Conte[1], M. Vecchi[1], M. Fraquelli[1]

[1] *Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milano, Italy*
[2] *Department of Biomedical and Clinical Sciences, Ospedale Luigi Sacco, Università degli Studi di Milano, Milan, Italy*
[3] *Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Interventional Radiology, Università degli Studi di Milano, Milan, Italy*

Introduction: Hepatic venous pressure gradient (HVPG) is the reference standard for the assessment of portal hypertension (PH). Liver stiffness (LS) has a correlation with PH, but not optimal with its severity. Spleen stiffness (SS) could be an alternative in prediction of PH presence and severity.

Aim: To assess feasibility and reproducibility of SS measured by Elast-PQ Shear Wave Elastography (pSWE) in patients with chronic liver disease (CLD) and to investigate the accuracy of SS to predict PH in cirrhotics.

Methods: First cohort: 186 CLD patients enrolled. In the same day they underwent liver biopsy, abdominal ultrasound (US), SS measurement by Transient elastography (TE) and by SWE (2 different examiners). US, laboratory and clinical data were collected. Inter-rater agreement of SWE was evaluated by intraclass correlation coefficient (ICC), as 'poor' (0.00–0.19), 'fair' (0.20–0.39), 'moderate' (0.40–0.75) or 'excellent'(>0.75). Second cohort: we enrolled 80 cirrhotics. All underwent US, LS and SS by SWE, HVPG measurements and gastroscopy. Linear correlations between LS or SS and HVPG and linear regression analysis to find the determinants of HVPG > 12 were performed. p values < 0.05 as statistically significant.

Results: First cohort: 3.4% and 13.8% failure for SS measurement by SWE and TE, respectively. ICC between the 2 examiners was 0.74 (95% CI, 0.66–0.80). Second cohort: we had 2.5% and 48% failure for SS by SWE and TE, respectively. No linear correlation between HVPG and LS was found, whereas between HVPG and SS was significant ($p = 0.001$). At multivariate analysis SS values, alcoholic etiology, liver steatosis, portal flow < 18 cm/sec were significantly correlated with HVPG >12.

Conclusions: SS by SWE is feasible and reproducible in CLD patients and it can be applied in cirrhotics. SS is a promising tool both in the prediction of PH and as surrogate marker of HVPG decompensation threshold.

https://doi.org/10.1016/j.dld.2018.01.107

T-30

Is stiffness reliable for the detection of liver fibrosis in HCV patients treated with direct acting antiviral drugs (DAAs)? A prospective cohort study

S. Gaia [1], E. Vanni [1], D. Campion [1], E. Rolle [1], D. Stradella [1], P. Cortegoso Valdivia [1], A. Evangelista [2], A. Ciancio [1], A. Smedile [1], R. Trapani [1], G.M. Saracco [1]

[1] *Departement of Gastroenterology, AOU Città della salute e della Scienza di Torino, Turin, Italy*
[2] *Departement of Epidemiology, AOU Città della salute e della Scienza di Torino, Turin, Italy*

Aims: This study prospectively evaluates changes in liver fibrosis using non-invasive tests in chronic hepatitis C (CHC) patients undergoing DAAs.

Method: 180 CHC patients undergoing DAAs, were prospectively included. Before, after 3 and 12 months from the end of DAA, clinical, anthropometric, biochemical, elastographic and ultrasound (US) parameters (steatosis degree, bluntness of liver edges, irregularity of left lobe surface, S4 diameter) were collected. The CH-NISF score (an algorithm including ALT, PLTS, US parameters and liver stiffness by Fibroscan, available at http://health.mafservizi.it/NISF_Calculator/liver.htm) was calculated. A control group of 41 CHC subjects was included.

Results: All but one achieved SVR. ALT and GGT were significantly reduced after 3 and 12 months from DAAs ($p < 0.001$), whereas PLTS significantly increased ($p < 0.001$). Liver stiffness showed a significant improvement after therapy: 14.4 (11.4–21.5) *vs* 10.4 (7.3–16.1) *vs* 8.8 (6.7–13.6) KPa ($p < 0.001$). Notably, 54% were defined by Fibroscan as F4 before therapy, but only 19% remained F4 after 12 months from DAAs. None of the US fibrosis parameters changed, whereas liver US steatosis was significantly reduced after therapy ($p < 0.05$).

The mean probability by CH-NISF to be F3/F4 score was significantly reduced at 3 months after therapy ($75 \pm 32\%$ *vs* $69 \pm 35\%$; $p < 0.01$) and then stable at 12 months ($69 \pm 35\%$ *vs* $63 \pm 34\%$; p = ns). The mean probability to be F2 by CH-NISF was significantly reduced at 3 months ($15.3 \pm 21\%$ *vs* $10 \pm 13.5\%$; $p < 0.05$), and was stable at 12 months after therapy ($10 \pm 13.5\%$ *vs* $11.4 \pm 14\%$; p = ns).

Conclusion: In CHC patients a dramatic improvement of liver fibrosis by stiffness was significantly reduced early after DAA; conversely US fibrosis parameters and CH-NISF score seem to be little affected. We speculate that liver stiffness may be affected by the sudden decrease in liver inflammatory status. CH-NISF score or specific US parameters may be a better tool in estimating changes in liver fibrosis after DAAs.

https://doi.org/10.1016/j.dld.2018.01.108

T-31

Incidence and predictors of de novo hepatocellular carcinoma in HCV cirrhotic patients treated with direct-acting antivirals: A single-center prospective 3-year study

R. D'Ambrosio [1], E. Degasperi [1], M. Iavarone [1], A. Sangiovanni [1], A. Aghemo [2], R. Soffredini [1], M. Borghi [1], R. Perbellini [1], G. Lunghi [3], P. Lampertico [1]

[1] *CRC "A. M. e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[2] *Humanitas University Department of Biomedical Sciences, Rozzano-Milan, Italy*
[3] *Microbiology and Virology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

Background and aim: As the incidence of HCC in cirrhotics treated with anti-HCV direct-acting antivirals (DAAs) is controversial, we aimed to assess the incidence and predictors of de-novo HCC in DAA-treated HCV cirrhotics.

Methods: Consecutive HCV cirrhotics starting DAAs (November 2014–December 2016) at a single Center were enrolled. Exclusion criteria were CPT-C score, previous/active HCC or baseline undefined liver nodules. Cirrhosis was defined clinically, histologically or by liver stiffness (LSM). Baseline clinical features, biochemistry and non-invasive tests (NITs) of liver fibrosis (LSM, APRI, Fib-4, LSPS) were assessed.

Results: 510 HCV cirrhotics were enrolled: aged 63 (28–87) years, 60% males, 47% HCV-1b, 82% CPT A. LSM was 17.3 (12.1–75.0) kPa, APRI 2.0 (0.2–30.5), Fib-4 4.6 (0.3–46.3), LSPS 1.7 (0.3–29.0). An SVR was achieved by 96%. After 22 (1–36) months, de-novo HCC occurred in 24 (4.9%) patients, with a 3-year cumulative probability of 6% (95% CI 4–9%). HCC size was 18 (10–100) mm, 71% monofocal, 83% BCLC 0-A, 79% CPT A; AFP was 6 (1–57) ng/ml. At univariate analysis, de-novo HCC was associated with male gender ($p = 0.013$), diabetes ($p = 0.001$), baseline LSM (<0.0001) and LSPS (<0.0001). At multivariate analysis, in patients without available LSM ($n = 489$), male gender [HR 4.42 (95% CI 1.26–15.5), $p = 0.02$], diabetes [HR 3.59 (95% CI 1.57–8.23), $p = 0.002$] and Fib-4 [HR 1.08 (95% CI 1.01–1.15), $p = 0.018$] independently predicted HCC. In those with available LSM ($n = 404$), male gender [HR 10.0 (95% CI 1.33–75.7), $p = 0.025$], diabetes [HR 2.7 (95% CI 1.06–6.91), $p = 0.037$] and LSM [HR 1.03 (95% CI 1.01–1.06), $p = 0.004$] were significant. The 3-year cumulative probability of HCC was 8.7% in males *vs.* 1.6% females ($p = 0.005$), 18% in diabetics *vs.* 3.2% non-diabetics ($p = 0.0003$), 3.4% *vs.* 23% for LSM < or ≥30 kPa ($p < 0.0001$).

Conclusions: In a large, single-center prospective study of DAA-treated HCV cirrhotics, male gender, diabetes and NITs independently predicted HCC.

https://doi.org/10.1016/j.dld.2018.01.109

T-32

Progressive reduction of blood lysosomal acid lipase activity according to stage of adult chronic liver disease and altered enzymatic cellular distribution in cirrhosis

I. Mignini[1], M. Mischitelli[1], F. Angelico[2], A. De Santis[1], M.L. Attilia[1], F. Baratta[2], F. Ferri[1], D. Pastori[2], M. Del Ben[2], M. Pellone[1], S. Parisse[1], F. Piemonte[3], G. Tozzi[3], J. D'Amico[3], F. Violi[2], S. Ginanni Corradini[1]

[1] *Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy*
[2] *Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy*
[3] *Unit for Neuromuscular and Neurodegenerative Diseases, Children's Hospital and Research Institute "Bambino Gesù", Rome, Italy*

Lysosomal acid lipase (LAL), a key enzyme in lipid metabolism, is reduced in NAFLD compared to healthy controls (HC) and in cryptogenic cirrhosis compared to cirrhosis of other etiologies. We aimed to: compare whole blood LAL activity (WB-LAL) according to different stages and etiologies of chronic liver disease (CLD) and assess whether cirrhotics have a deficit of LAL in white blood cells (WBCs) and platelets (PLTs).

WB-LAL was measured by a fluorimetric method in: NASH/cryptogenic cirrhosis (NASH-C; $n=53$); HCV/alcoholic cirrhosis (HCV/A-C; $n=76$); histological NAFLD without cirrhosis (NAFLD; $n=47$); HCV/alcoholic chronic hepatitis (HCV/A-CH; $n=50$); HC ($n=37$). In 9 NASH-C, 7 HCV/A-C and 22 HC, LAL was also measured in isolated PLTs and WBCs.

Medians and interquartile ranges of WB-LAL were 0.54 [0.42–0.73], 0.65 [0.51–0.93], 0.77 [0.61–1.06], 0.97 [0.79–1.38] and 1.05 [0.85–1.42] nanomoles/spot/hour in the NASH-C, HCV/A-C, NAFLD, HCV/A-CH, and HC group, respectively. At logistic regression, independently from age, gender and BMI, low WB-LAL was associated with: a) NASH-C compared to NAFLD (OR 0.063; CI95% 0.009–0.420; $P=0.004$) and b) NAFLD compared to HCV/A-CH (OR 0.077; CI95% 0.013–0.450; $P=0.004$). Low WB-LAL was associated with HCV/A-C compared to HCV/A-CH (OR 0.107; CI95% 0.025–0.457; $P=0.003$), independently from age, gender, BMI, amount and years of daily alcohol consumption at risk for cirrhosis development and years since HCV-infection. WB-LAL did not differ between HCV/A-CH and HC. Intracellular PLT's LAL was significantly ($P<0.001$) reduced in cirrhotics compared to HC (11.75[3.23–42.55] vs 65.90[44.43–91.85] nanomoles/mg protein/hour), while no intergroup difference was found in WBCs activity.

In fatty liver disease, as disease worsens, WB-LAL is progressively reduced at all stages. In HCV and alcoholic CLD, low WB-LAL is associated only with the cirrhotic stage. Cirrhotics have reduced intracellular LAL in PLTs. We hypothesize that reduced LAL in PLTs may play a role in CLD pathophysiology, and especially in fatty liver disease.

https://doi.org/10.1016/j.dld.2018.01.110

T-33

Fibroscan liver stiffness (LMS) and controlled attenuation parameter (CAP) in the evaluation of cardiovascular risk assessment in patients with NAFLD

R. Lombardi[1], S. Petta[2], A. Giannetti[2], R. Boemi[2], G. Pisano[1], C. Bertelli[1], A. Craxi[2], S. Fargion[1], A.L. Fracanzani[1]

[1] *Department of Pathophysiology and Transplantation Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy*
[2] *Department of Gastroenterology and Hepatology DI.Bi.M.I.S University of Palermo, Italy*

Introduction: Non-alcoholic fatty liver disease (NAFLD) may progress to advanced fibrosis and exposes to high cardiovascular mortality. FibroScan® detect hepatic steatosis and fibrosis, but its role in defining a cardiovascular risk profile is still unexplored.

Aim: To evaluate if FibroScan® is able to detect NAFLD patients at higher cardiovascular risk.

Method: 433 biopsy proven NAFLD were enrolled in two Italian liver centers. All patients underwent FibroScan®, carotid Doppler US and echocardiography. Controlled attenuation parameter (CAP) value ≥248 dB/m and liver stiffness (LSM) ≥7.9 kPa defined the presence of steatosis and significant fibrosis, respectively.

Results: Mean age was 50 ± 14 years and 66% patients were males. Prevalence of diabetes was 29%, hypertension 38%, dyslipidemia 54%, 24% of whom on statins. Carotid plaques were present in 45%, mean IMT was 0.8 ± 0.2. Mean epicardial adipose tissue was 7.5 ± 2.5 mm, diastolic dysfunction (E/A < 1) was present in 33%. Only 4% patients reported cardiovascular events. LSM ≥7.9 kPa was present in 195 patients (45%) and at univariate analysis correlated with carotid plaques ($p<0.001$), IMT ($p=0.007$), diastolic dysfunction ($p<0.001$) and cardiovascular events ($p=0.004$), at multivariate analysis LSM ≥7.9 kPa remained independently associated with age (OR 1.055; 95% CI 1.001–1.111), waist circumference (WC) (OR 1.047; 95% CI 1–1.096), plasmatic insulin (OR 1.058; 95% CI 1.005–1.114) and histology stage F2 (OR 4.949; 95% CI 1.858–13.182), and CAP ≥248 dB/m with severe histology steatosis and inflammation (OR 7.9, 95%CI 1.6–63 and OR 6.4, 95%CI 1.01–126). Differently from fibrosis, defined by LSM, histological fibrosis was independently associated with IMT and history of cardiovascular events.

Conclusion: Transient elastography confirms its association with metabolic parameters, showing a good correlation with histology. Our results indicate that FibroScan® is unable to detect NAFLD patients at higher cardiovascular risk, suggesting a complex and multifactorial underlying scenario predisposes to the cardiovascular disease.

https://doi.org/10.1016/j.dld.2018.01.111

T-34

Excellent effectiveness of direct-acting antivirals for HCV treatment in patients with cirrhosis: Analysis of 3345 patients from the Lombardia Network

E. Degasperi[1], L. Pasulo[2], A. Aghemo[3], M. Puoti[4], S. Zaltron[5], F. Maggiolo[6], G. Rizzardini[7], S. Fargion[8], P. Sacchi[9], R. Gulminetti[9], M. Zuin[10], T. Quirino[11], M.G. Rumi[12], A. Pan[13], P. Grossi[14], A. Rossini[15], A. Corbellini[16], C. Uberti Foppa[17], A. Colli[18], P. Lampertico[1], S. Fagiuoli[2], on behalf of the NAVIGATOR II study group

[1] *CRC "A. M. e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[2] *Gastroenterology, ASST Papa Giovanni XXIII, Italy*
[3] *Humanitas University Department of Biomedical Sciences, Rozzano-Milan, Italy*
[4] *Infectious Diseases ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[5] *Infectious Diseases, Spedali Civili, Brescia Bergamo, Italy*
[6] *Infectious Diseases, ASST Papa Giovanni XXIII, Bergamo, Italy*
[7] *Infectious Diseases, Sacco Hospital, Italy*
[8] *Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[9] *Infectious Diseases, Policlinico Pavia, Italy*
[10] *Gastroenterology, San Paolo Hospital, Milan, Italy*
[11] *Infectious Diseases, Busto Arsizio Hospital, Varese, Italy*
[12] *Hepatology, San Giuseppe Hospital, Milan, Italy*
[13] *Infectious Diseases Cremona Hospital, Italy*
[14] *Infectious Diseases Varese Hospital, Italy*
[15] *Hepatology, Spedali Civili, Brescia Bergamo, Italy*
[16] *Infectious Diseases Vizzolo Predabissi Hospital, Italy*
[17] *Immunology and Infectious Diseases, San Raffaele Hospital, Milan, Italy*
[18] *Internal Medicine, Lecco Hospital, Lecco, Italy*

Background and aim: As real-life data in hepatitis C virus (HCV) cirrhotics treated with direct-acting antivirals (DAA) are limited in Italy, we evaluated the effectiveness of DAA in patients with cirrhosis from a large Italian Network.

Methods: Consecutive HCV cirrhotics not listed for liver transplantation (AIFA criterion 1) starting DAA during 2014–2017 in 34 hepatology centres with available sustained virological response (SVR12) data were enrolled.

Results: 3345 patients were analysed: mean age was 61 (21–90) years, 65% males, BMI 25 (15–48); mean ALT 85 (12–595) U/L, platelets 114 (12–574) $\times 10^3$/mL, AFP 9 (2–322) ng/ml, LSM 20.0 (12.1–75.0) kPa. HCV genotype was 1 in 62%, with median HCV-RNA 726,500 (56–31,340,000) IU/ml. 33% patients were IFN-experienced, and CPT was A in 73% patients. 176 (5%) had a history of hepatocellular carcinoma (HCC): they were older than HCC-free patients ($p < 0.0001$) but similar according to the other clinical characteristics. Most used regimens were Sofosbuvir (SOF)/Ledipasvir ± Ribavirin (RBV) in 30%, Paritaprevir/Ombitasvir-ritonavir ± Dasabuvir ± RBV in 21%, SOF + Simeprevir ± RBV in 17%, SOF + Daclatasvir ± RBV in 16%, SOF + RBV in 14%. Complete data on SOF/Velpatavir and Elbasvir/Grazoprevir treatment were available for 3% of patients, only. Overall, 78% of patients received a RBV-containing regimen. An SVR was achieved by 95% patients, the lowest SVR rates being observed in HCV-3 (90% *vs.* 97% HCV-1, 94% HCV-2, 94% HCV-4, $p < 0.00001$). SVR rates were independent on RBV use ($p = 0.17$), but lower in patients with CPT-B cirrhosis (91% *vs.* 96%, $p = 0.01$) and previous HCC history (100% vs. 95%, $p = 0.001$). In HCV-3 patients, SVR rates were suboptimal following SOF + RBV, but not SOF + DCV (77% *vs.* 95%, $p < 0.0001$); RBV addition to SOF + DCV provided additional efficacy (86% *vs.* 96%, $p = 0.02$).

Conclusions: DAA-based treatments provide excellent cure rates also in patients with cirrhosis

https://doi.org/10.1016/j.dld.2018.01.112

T-35

Filamin A expression predicts early recurrence of hepatocellular carcinoma after hepatectomy

M. Donadon[1], L. Di Tommaso[2], C. Soldani[1], B. Franceschini[1], E. Vitali[3], M. Roncalli[2], A. Lleo[4], A. Lania[3], G. Torzilli FACS[1]

[1] *Department of Department of Biomedical Sciences, Hepatobiliary and General Surgery, Via Manzoni 56, 20089, Rozzano, Milan, Italy*
[2] *Department of Biomedical Sciences, Pathology, Via Manzoni 56, 20089, Rozzano, Milan, Italy*
[3] *Department of Biomedical Sciences, Endocrinology, Via Manzoni 56, 20089, Rozzano, Milan, Italy*
[4] *Department of Biomedical Sciences, Internal Medicine and Hepatology, Humanitas University, Humanitas Clinical and Research Center, Via Manzoni 56, 20089, Rozzano, Milan, Italy*

Background: The risk of recurrence of hepatocellular carcinoma (HCC) after hepatectomy is very high and predictive markers of early recurrence (ER) are not available. The overexpression of Filamin A (FLNA), a cytoskeleton protein with scaffolding properties, has recently been associated with progression in different tumors. The aim of this study was to test the expression of FLNA in a cohort of patients operated for HCC.

Methods: A retrospective cohort of patients who underwent curative hepatic resection at Humanitas Clinical and Research Center between January 2004 and December 2014 was analyzed. FLNA was tested using a tissue-microarray in the extra-tumoral, peritumoral, and intra-tumoral tissue compartments. The endpoint was the role of FLNA expression in predicting ER of HCC after hepatectomy. Analyses were performed according to the REMARK guidelines.

Results: A total of 113 patients were included in the study. FLNA was expressed only in the peri-tumoral and intra-tumoral tissue but not in the extra-tumoral normal tissue. Several variables, including T-stage, tumor number, tumor size, type of viral hepatitis, type of hepatectomy, and intra- and peri-tumoral immune-reactivity to FLNA were significantly associated with ER by univariate analysis. With multivariate analysis, only T-stage (HR = 2.108; $p = 0.002$), tumor number (HR = 1.586; $p = 0.023$), intra-tumoral (HR = 2.672; $p < 0.000$) and peri-tumoral immune-reactivity to FLNA (HR = 2.569; $p < 0.000$), significantly correlated with ER. The logistic regression analysis revealed that advanced T-stage (OR = 2.985; $p = 0.001$), HCV-infection (OR = 1.219; $p = 0.008$), and advanced tumor grading (OR = 2.781; $p = 0.002$) were associated with intra-tumoral FLNA immune-reactivity.

Conclusions: FLNA expression predicts recurrence of HCC after hepatectomy. This finding provides important insights that would

help physicians to personalize follow-up strategies and develop a new therapeutic target.

https://doi.org/10.1016/j.dld.2018.01.113

T-36

Prognostic role of BAP1 and PBRM1 expression in intrahepatic cholangiocarcinoma

S. Sarcognato [1], E. Gringeri [2], M. Fassan [1], M. Di Giunta [2], V. Guzzardo [1], U. Cillo [2], M. Guido [1]

[1] *Department of Medicine – DIMED, University of Padova, Padova, Italy*
[2] *Department of Surgery, Oncology and Gastroenterology, Hepatobiliary Surgery and Liver Transplantation Unit, Padova University Hospital, Padova, Italy*

Introduction: Intrahepatic cholangiocarcinoma (iCC) has universally poor outcome, mainly due to its late clinical presentation. Identification of specific biomarkers and development of effective treatment are still urgently required.

Mutations in *PBRM1* and *BAP1* genes have been related to survival in iCC patients. miR-31-5p seems also to play important regulatory functions in iCC and it directly regulates BAP1 expression in lung cancer.

Aim: In this study, tissue expression of BAP1, PBRM1, and miR-31 was investigated in iCC and correlated with clinical-pathological features.

Materials and methods: Sixty-one consecutive patients who underwent curative hepatic resection for iCC were enrolled. None received any therapy prior to surgery. Immunostaining for BAP1 and PBRM1, and *in situ* hybridization for miR-31 were performed, using tissue microarray slides.

Results: A strong expression of BAP1 and PBRM1 was associated with a reduced overall ($p = 0.04$ and $p = 0.002$, respectively) and disease-free ($p = 0.05$ and $p = 0.02$, respectively) survival. High levels of miR-31 were significantly associated to a low expression of BAP1 protein ($p = 0.03$). A trend of association between an overexpression of PBRM1 and the presence of perineural invasion was also observed ($p = 0.07$).

Conclusions: In iCC, overexpression of BAP1 and PBRM1 is related to a poor prognosis and miR-31 may act as a direct regulator of BAP1.

https://doi.org/10.1016/j.dld.2018.01.114

T-37

Pattern of hepatocarcinoma recurrence in cirrhosis: The role of anatomic and parenchyma-sparing resection. A propensity score analysis

S. Famularo [1,2], S. Di Sandro [3], A. Giani [1,2], A. Lauterio [3], F. Romano [1,2], V. Buscemi [3], F. Uggeri [1,2], R. De Carlis [3], L. Gianotti [1,2], L. De Carlis [1,3]

[1] *School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy*
[2] *Department of Surgery, San Gerardo Hospital, Monza, Italy*
[3] *Department of General Surgery and Transplantation, Niguarda Ca' Granda Hospital, Milan, Italy*

Background: Disease recurrence mechanisms after surgical resection for hepatocarcinoma are still poorly understood. Further investigations on this matter may offer additional elements for more personalized therapeutic strategies. The aim of the study was to investigate the role of anatomic resection (AR) and parenchyma-sparing resection (PSR) on the patterns of disease recurrence.

Materials and methods: From a prospectively maintained dataset we retrieved data of 384 cirrhotic patients with a first diagnosis of hepatocarcinoma. They were stratified for AR (142; 37%) and PSR (242; 63%). At baseline, the two groups diverged for several variables. A propensity score analysis with a caliper of 0.1 was used to reduce the risk of selection bias leaving 200 patients correctly matched (100 in AR and 100 in PSR) for the final analysis.

Results: After matching, there were no differences between groups. Fifty-nine patients (62.8%) had recurrence after AR, while fifty-eight (63.7%) after PSR ($p = 0.891$). The rates of recurrence on the resected margin were 15.3% and 15.5% for AR and PSR respectively ($p = 0.968$). Median disease-free survival (DFS) was 18.6 months (95%CI: 14.1–23.2) and 20.0 months (95% CI: 14.3–25.67) for AR and PSR respectively ($p = 0.914$). The rate of early recurrence (within 24months) were 29% for AR and 37% for PSR ($p = 0.417$). When it is considered patients with microvascular invasion, median DFS was 10.72 months (95%CI: 3.43–18.01) for AR, and 9.44 months (95%CI: 5.01–13.86) for PSR (p:0.607). Moreover, when the early-recurrence is taking into account in this sub-group, no significant evidence on DFS was evident between groups (p:0.417).

Conclusions: The excision of the anatomic segment does not seem to be related with the reduction of recurrence rate in cirrhotic patients.

https://doi.org/10.1016/j.dld.2018.01.115

T-38

Serum and bile squamous cell carcinoma antigen detection: A new prognostic marker in patients with perihilar cholangiocarcinoma

E. Gringeri[1], M. Di Giunta[1], A. Biasiolo[2], M. Ruvoletto[2], G. Villano[2], L. Zarantonello[1], P. Pontisso[2], U. Cillo[1]

[1] *Hepatobiliary Surgery and Liver Transplantation Unit, University of Padova, Italy*
[2] *Departement of Medicine, University of Padova, Italy*

Introduction: Serum and bile tumor markers are increasingly investigated for the diagnosis and prognosis of malignant biliary structures. Cholangiocarcinoma (CCA) and hepatocellular carcinoma (HCC) can both derive from liver stem-progenitor cells and this cell compartment expresses high levels of Squamous cell carcinoma antigen (SCCA). The aim of our study was to investigate serum and bile levels of SCCA in patients with perihilar cholangiocarcinoma (pCCA).

Methods: From March 2015 and May 2017 a population of 32 patients (19 with pCCA and 13 controls) was evaluated. The diagnosis of pCCA was based on a combination of clinical, biochemical, radiological or pathological findings. Demographic data, patient history and medications were recorded. Clinical signs, liver function tests, surgical procedures and follow-up were collected in a prospective database. Bile and serum were collected during surgery and were transported to the processing laboratory within 1 h, aliquoted and stored at −20 °C until analysis. The concentration of free SCCA and of SCCA-IgM immune complexes levels were measured by commercial assays (HepaLisa and Hepa-IC, respectively, Xeptagen, Venice, Italy) following manufacturer's instructions. The cut-off for free SCCA bile levels, free SCCA serum levels and SCCA-IgM immune complexes were 3.88 ng/mL, 3.1 ng/mL and 160 AU/mL, respectively.

Results: The median overall survival of pCCA patients with positive free serum SCCA concentration was significantly reduced compared to negative patients (144 vs 614 days; $p = 0.048$). Free SCCA serum levels showed a better sensitivity and specificity, respect to SCCA-IgM immune complexes and SCCA bile (75% and 66% vs 12% and 66% and vs 30% and 55%, respectively) to identify patients with reduce survival.

Conclusion: These prelimary findings suggest that free SCCA in serum concentrations could become a promising prognostic marker in patients with pCCA, supporting clinical decisions in this oncological setting

https://doi.org/10.1016/j.dld.2018.01.116

T-39

Use of a new type of controlled expansion stent in the creation of Transjugular Intrahepastic Portosystemic Shunt for the treatment of severe portal hypertension. A single center experience with 1 year follow-up

I. Petridis[1], A. D'Antoni[1], G. Pietrosi[1], L. Maruzzelli[2], R. Miraglia[2], A. Luca[2], R. Volpes[1]

[1] *Hepatology and Gastroenterology Unit, IRCCS ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies), Palermo, Italy*
[2] *Department of Diagnostic and Therapeutic Services, IRCCS ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies), Palermo, Italy*

Background and aims: Transjugular Intrahepatic Portosystemic Shunt (TIPS) is a valid option for the treatment of complications in liver cirrhosis. Portosystemic encephalopathy (PSE) is a side effect and studies showed that it could be prevented by using underdilated stents. With the present study we want to bring our personal experience in the use of a controlled expansion stent in TIPS creation (GORE® VIATORR® VTX).

Methods: 38 patients with severe PH underwent TIPS using a VTX stent. Clinical/laboratoristic data and Duplex ultrasonography were assessed the day before and after the TIPS and then at 4, 12 and 24 weeks after the TIPS.

Results: Main indication to TIPS was refractory ascites in 29 pts and gastrointestinal bleeding in 5. Follow-up after TIPS varied from 2 to 14 months. Technical success was 100% and no complications were reported. In 37 pts stent was dilated to 8 mm of diameter and significant reduction of the porto-caval pressure gradient (PPG) was obtained in all pts. Mean PPG value pre-TIPS was 16.05 mmHg and post-TIPS 6.61 mmHg. PSE emerged in 10 pts (26%). In 16 pts thrombosis of the portal system was present before the TIPS and it was resolved in 13 (81.25%). Clinical response was 75.86% for refractory ascites (22 pts) while no recurrence of bleeding episodes were registered and only 2 pts needed a further session of dilation of the stent from 8 to 10 mmHg (persistent ascites). Although it was noticed a mild increase at the MELD score at 3 and 6 months post-TIPS, this data was not associated with a worsened Child-Pugh score. 4 pts died because of septic episodes and 3 pts underwent liver transplant.

Conclusions: TIPS creation using controlled expansion stent can be safely performed in patients with severe portal hypertension and is associated with good clinical response and outcome.

https://doi.org/10.1016/j.dld.2018.01.117

T-40

Risk and outcome of hepatitis B virus (HBV) reactivation during chronic hepatitis C treatment with direct-acting antivirals (DAAs) in patients with HCV-related advanced fibrosis: A single-center experience

R. D'Ambrosio [1], E. Degasperi [1], A. Aghemo [1], M. Borghi [1], R. Perbellini [1], S. De Nicola [2], G. Lunghi [3], P. Lampertico [1]

[1] *CRC "A. M. e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[2] *Hepatology and Gastroenterology Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[3] *Microbiology and Virology Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy*

Background and aim: Hepatitis B virus (HBV) reactivation following anti-hepatitis C virus (HCV) treatment with direct-acting antivirals (DAAs) has been described in patients with HBV/HCV coinfection or resolved HBV infection, however studies in patients with advanced fibrosis are lacking. Therefore, we investigated prevalence and outcome of HBV reactivation (HBV-R) in a large cohort of DAA-treated HCV patients with advanced fibrosis.

Materials and methods: All consecutive DAA-treated patients with advanced HCV fibrosis were prospectively enrolled. HBV/HCV coinfection was defined as detectable HCV-RNA and HBsAg positivity; resolved HBV infection as HBsAg negativity and anti-HBc positivity (± anti-HBs). Fibrosis was staged clinically, histologically (METAVIR F3 or F4) or according to liver stiffness (LSM > 10 kPa or >11.9 kPa). HBV-R was defined as an increase of HBV-DNA > 1 Log IU/ml in HBV/HCV patients, and as HBsAg seroreversion ± detectable HBV-DNA in anti-HBc patients.

Results: Between 2015 and 2016, 692 F3-F4 patients started DAAs. They were males (60%), aged 63 (23–89), 76% cirrhotics, with baseline LSM of 14 (9.0–75.0) kPa. HCV genotype was 1 in 62% and baseline HCV-RNA was 581,270 (764–13,333,872) IU/ml. 301 (43%) were anti-HBc positive. Overall SVR rates were 96%. HBV/HCV patients were 10 (1.4%), 100% HBeAg negative, 60% males, 70% cirrhotics, with LSM of 21 (9–43.5) kPa. Baseline HBV-DNA undetectable in 5, 4 (80%) on anti-HBV nucleot(s)ides (NUCs). After 2 weeks of DAA, HBV-R occurred in 3 (50%) NUC-free patients: at reactivation, ALT was 21 (18–52) U/l, HBV-DNA was 330 (248–6915) IU/ml, HBsAg was 62 (1.1–1329) UI/mL and HCV-RNA was 148 (18–389) IU/mL. No clinical decompensation were recorded. NUC was started in all cases: HBV-DNA became undetectable after 8 (6–39) weeks, whilst HBsAg was lost in one patient. No HBV-R was observed among anti-HBc positive patients.

Conclusions: HBV-R is frequent among HBV/HCV patients but not among HCV patients with resolved HBV infection.

https://doi.org/10.1016/j.dld.2018.01.118

Digestive and Liver Disease 50(1S) (2018) 42–61

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Abstracts of the 51st A.I.S.F. – Italian Association for the Study of the Liver – Annual Meeting 2018 Rome, February 22nd–23rd, 2018: Selected Posters Friday

F-01

Low levels of squamous cell carcinoma antigen–IgM complexes in serum are predictors of better survival in patients with liver cirrhosis

M. Cagnin[1], A. Biasiolo[1], A. Gallotta[2], A. Martini[1], M. Ruvoletto[1], S. Quarta[1], S. Fasolato[1], P. Angeli[1], G. Fassina[2], P. Pontisso[1]

[1] *Internal Medicine and Hepatology, Regional Referral Center for Liver Disease, Department of Medicine, University of Padua, Italy*
[2] *Xeptagen SpA, Venice, Italy*

Introduction: Cirrhosis is a major cause of morbidity and mortality worldwide, especially due to HCC occurrence. The lack of reliable biomarkers affects screening algorithms for HCC, even in selected patients. The identification of patients with aggressive progression of liver disease and the early diagnosis of HCC are of paramount importance in clinical practice. Several studies have shown that in patients with cirrhosis high levels of squamous cell carcinoma antigen–IgM (SCCA–IgM) complex are associated with HCC development and in patients with HCC this biomarker has been found correlated with poor survival.

Aim: To assess the behaviour of SCCA–IgM in patients with cirrhosis in relation to clinical outcome and patient survival.

Material and methods: Sera collected at presentation from 100 patients with cirrhosis, enrolled from April 2007 to December 2012 in a prospective study (FIRB Prot. RBLA03S4SP_005) were analyzed. None of the patients had evidence of HCC at the time of inclusion in the study. Patients were regularly followed and clinical data and imaging information were recorded. SCCA–IgM was determined in serum using a commercially available ELISA kit (Hepa-IC, Xeptagen S.p.A, Venice, Italy).

Results: Patients with SCCA–IgM levels <100 AU/ml at baseline showed significantly higher survival than patients with values >100 AU/ml (median values: 107 vs 68 months, $p = 0.049$). These features were independent from etiology and the major complication in patients with SCCA–IgM levels >100 AU/ml was HCC development. Other cirrhosis complications were not related with the behavior of this biomarker.

Conclusions: Low SCCA–IgM levels in serum have been shown to be a strong predictor of better survival in patients with cirrhosis, mainly due to the lower risk of HCC development. These findings might be useful in clinical practice, to better tailor the personalized timing of surveillance in individual patients with cirrhosis.

https://doi.org/10.1016/j.dld.2018.01.039

F-02

Primary biliary cholangitis (PBC): The patient journey to diagnosis and through the disease

A. Floreani[1], B. Marini[2], S. Provisione[2], C. Bassanelli[2], E. De Santis[3], N. Cazzagon[1], M. Margotti[4], P. Andreone[4], L. Muratori[4], P. Invernizzi[5], M. Marzioni[6], A. Benedetti[6], D. Alvaro[7], V. Calvaruso[8], A. Craxì[8]

[1] *Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy*
[2] *Intercept Italia srl, Milan, Italy*
[3] *GFK Italia srl, Milan, Italy*
[4] *Department of Medical and Surgical Science, University of Bologna, Bologna, Italy*
[5] *Department of Medicine and Surgery, University of Milan Bicocca, Milan, Italy*
[6] *Clinics of Gastroenterology, Univerità Politecnica delle Marche, Ancona, Italy*
[7] *Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy*
[8] *Clinics of Gastroenterology, Univerità Politecnica delle Marche, Ancona, Italy; Gastroenterology and Epatology, DIBIMIS, Università di Palermo, Palermo, Italy*

Introduction: Primary biliary cholangitis (PBC) is a rare cholestatic liver disease that may progress to liver decompensation and death. Due to its epidemiological characteristics and natural history, diagnosis may be delayed and the burden of disease underestimated.

Aim: The aim of this research is to gather patient insights on their emotional experience as patients and to identify gaps in disease management.

Method: Patients from 7 Italian tertiary care centers were asked to participate in a survey exploring 5 domains: journey to diagnosis, disease burden and management, HCP-patient relationship, patient expectations.

Results: Eighty-six patients were included. Time from symptoms onset to first visit and time from first visit to diagnosis averaged 2 years for both; first point of contact was the General Practitioner for 56% of patients; over 40% perceived the journey to diagnosis as difficult. Fatigue, dyspeptic syndrome and headache were found to be symptoms with a more negative impact on daily life. Pruritus had been reported by 59% of patients, while only 28% consider it as negatively impacting their daily life. Diagnosis had a negative impact on social life in about 20%. Patients diagnosed with PBC missed 15 working days/year specifically due to the disease. Attitudes related to disease acceptance vary within patients; however, a general concern on future impact on their life remains. Specialist is considered as a reliable interlocutor, but patients do not feel that enough information is available about their disease.

Conclusions: These results represent the first attempt to capture the PBC patient perspective in a real-world patient care setting in Italy. The diagnosis of PBC negatively affected a patient's life, not only in terms of symptoms of disease progression, but also from an emotional perspective. The data suggested that there is a need to improve the management of PBC patients especially in terms of diagnosis, emotional support and communication.

https://doi.org/10.1016/j.dld.2018.01.040

F-03

Acquisition of stem-like features in human cholangiocarcinoma is associated with an oxidative glucose metabolism

C. Raggi [1], N. Navari [1], M.L. Taddei [2], E. Sacco [3,4], M. Correnti [5], I. Orlandi [3,4], P. Chiarugi [2], F. Marra [1]

[1] *Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Florence, Italy*
[2] *Dipartimento di Scienze Biomediche, Sperimentali e Cliniche, Università degli Studi di Firenze, Florence, Italy*
[3] *SYSBIO, Centre of Systems Biology, Milan, Italy*
[4] *Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milan, Italy*
[5] *Center for Autoimmune Liver Diseases, Humanitas Clinical and Research Center, Rozzano, Italy*

Background and aims: Cholangiocarcinoma (CCA) is a severe and mostly intractable cancer. Cancer stem cells (CSC) are resistant to drugs and responsible for tumor initiation and relapse. However, mechanisms underlying CCA-CSC state remain largely unknown. Growing lines of evidence support the idea that deregulated cellular metabolism is linked to acquisition of tumor stem-like properties and drug resistance. Indeed, both components of glycolytic and mitochondrial pathways are involved in altered metabolism linked to chemoresistance of several cancers. The present study aimed to explore alterations of glucose metabolism in CCA stem-scenery.

Method: Stem-like compartment was enriched by sphere culture (SPH) in established human intrahepatic CCA cells (HUCCT1, CCLP1, SG231). CCA-SPH extracellular flux analysis was examined by seahorse technology. CCA-SPH expression of Hexokinase II (HKII), pyruvate kinase M1 (PKM1), PKM2 and PGC-1α was investigated by western bottling. Metformin effect on survival was examined by MTT. Glucose uptake was quantified by incorporated (U-14C) deoxy-D-glucose amount.

Results: In contrast to parental cells grown as adherent monolayers (MON), metabolic analyses by seahorse technology revealed a CCA-SPH more efficient respiratory phenotype by mitochondrial oxidative phosphorylation (OXPHOS). Consequently, targeting mitochondrial complex I by metformin administration, CCA-SPH survival was impaired. In accordance, CCA-SPH cells showed downregulation of glycolytic marker HKII indicating adaptation toward mitochondrial respiration in order to acquire a metabolic advantage. Also, PKM1 overexpression and PKM2 repression in CCA-SPH cells correlated with repression of the pentose phosphate pathway and promotion of stem-like phenotype. Finally, over-expression of PGC-1α in CCA-SPH indicated that mitochondrial biogenesis and respiration was functionally relevant in CCA stem-like cells.

Conclusion: Our findings suggest that CCA stem-like cells undergo a metabolic reprogramming resulting in OXPHOS addiction to meet energy demands. Indeed OXPHOS inhibition might represent a novel therapy strategy to achieve treatment response in human CCA.

https://doi.org/10.1016/j.dld.2018.01.041

F-04

Extracellular signal-regulated kinase 5 (ERK5) regulates growth, migration and invasion of cholangiocarcinoma (CCA) cells

A. Gentilini, A. Caligiuri, G. Di Maira, M. Pastore, E. Rovida, F. Marra

University of Florence, Italy

Background and aims: Epidermal growth factor (EGF) contributes to cholangiocarcinoma (CCA) development and progression. The extracellular-signal regulated kinase ERK5 pathway, a member of the MAPK family, is involved in the pathogenesis of cancer. Additionally, ERK5 is implicated in cytoskeletal remodeling and cell motility. The purpose of the present study was to investigate the expression and the role of ERK5 in CCA cells.

Methods: The intrahepatic cholangiocarcinoma cell line HuCCT-1, was used in this study. Cell motility and invasion were assessed using modified Boyden chambers. Cell growth was determined by cell counting and BrdU incorporation assay. P-ERK5, p27, PARP, Cyclin E and Caspase 3 protein expressions were investigated by Western blotting. Cell cycle analysis was conducted by FACScan Silencing of cells was performed using shRNA.

Results: P-ERK5 was upregulated by cell exposure to EGF and Medium. Two specific pharmacologic inhibitors, XMD8-92 and AX 15836 were used to inhibit ERK5 activity. EGF- and complete medium -induced survival, migration and invasion were reduced by XMD8-92, at the doses of 5 μM and 10 μM. BrdU incorporation assay showed an inhibition of DNA synthesis in cells treated with XMD8-92. Cell cycle analysis showed more prolonged G0/G1 phases in cells treated with XMD8-92 compared to control. Moreover P27 protein expression resulted increased by this inhibitor at 24 h while cyclin E was inhibited. PARP protein expression decreased and caspase 3 too in cells treated with XMD8-92, confirming a block of the cell cycle by this molecule. AX 15836, a more specific inhibitor of ERK5 activity confirmed an important role of this protein in EGF- and complete medium-induced chemotaxis and invasion. In cells silenced for ERK5, growth, survival, invasion and migration were inhibited respect to control.

Conclusion: In HuCCT-1 cells, ERK5 activity plays an important role in mediating HuCCT-1 growth, survival and motility.

https://doi.org/10.1016/j.dld.2018.01.042

F-05

The ALBI and p-ALBI grades predict survival in patients with hepatocellular carcinoma undergoing transarterial chemoembolization (TACE)

C. Campani[1], A. Vitale[2], G. Dragoni[1], S. Aburas[1], U. Arena[1], E.G. Giannini[3], F. Trevisani[4], F. Marra[1], for the Ita.Li.Ca. study group

[1] *Università di Firenze, Italy*
[2] *Università di Padova, Italy*
[3] *Università di Genova, Italy*
[4] *Università di Bologna, Italy*

Background and aims: The prognosis of hepatocellular carcinoma is influenced by severity of liver dysfunction. Child–Pugh (CPS) and MELD scores have considerable limitations. Recently, the prognostic value of albumin-bilirubin (ALBI) grade has been evaluated in patients undergoing HCC treatment with different modalities, but not specifically in patients undergoing TACE. Moreover, the pALBI grade that includes platelet count, is a surrogate marker of portal hypertension.

Method: We retrospectively evaluated the prognostic significance of ALBI and pALBI in patients undergoing TACE recorded in the Ita.Li.Ca. database, and compared it with other prognostic systems, including MELD, CPS, hepatoma arterial-embolization prognostic (HAP) and mHAPII.

Results: 2283 TACE performed in 1012 consecutive patients were evaluated. Patients had a median MELD of 9 and belonged to all BCLC stages. Median overall survival in the whole population was 33.9 months. Considering all TACE procedures, the ALBI and pALBI grades were predictors of overall survival ($p < 0.001$), similar to the HAP and the mHAP scores. ALBI was a significant predictor of OS only in BCLC-C patients ($p < 0.001$), while pALBI was a significant predictor of OS in BCLC-B ($p < 0.001$) and BCLC-C ($p < 0.001$), similar to HAP and mHAPII. Similar data were obtained when only the first TACE was considered (1012 patients, 520 BCLC-A, 299 BCLC-B and 193 BCLC-C). ALBI was a significant predictor of overall survival ($p < 0.001$) similar to the pALBI, HAP and mHAPII scores ($p < 0.003$). When different BCLC stages were considered, ALBI, pALBI and HAP were significant predictors of OS in BCLC-C, whereas mHAPII was not significant. pALBI was also a significant predictor of OS in BCLC-B.

Conclusion: ALBI and pALBI offer additional simple and objective methods of assessing liver function in HCC and may be useful for selecting patients more likely to survive after TACE, especially ALBI in the BCLC-C stage and pALBI in BCLC-B and BCLC-C stages.

https://doi.org/10.1016/j.dld.2018.01.043

F-06

Influence of DAA treatment on waitlisting and transplant rate for HCV related disease: Preliminary results of a single center experience

C. Iegri[1], L. Pasulo[1], M. Colpani[1], F. Leonardi[1], M. Colledan[2], M.G. Lucà[1], N. Pinelli[2], A. Ghirardi[3], S. Fagiuoli[1]

[1] *Division of Gastroenterology, Hepatology and Transplantation, Papa Giovanni XXIII Hospital Bergamo, Italy*
[2] *Department of Surgery, Papa Giovanni XXIII Hospital Bergamo, Italy*
[3] *FROM Foundation, Papa Giovanni XXIII Hospital Bergamo, Italy*

Background and aim: The availability of DAAs has allowed the treatment of HCV infection in the setting of OLT either before, during the waiting period and after LT. Therefore, a reduction of HCV prevalence, a relative increase of HCV transplant for HCC rather than ESLD and increasing waitlist removal for improvement should be expected. We aimed to assess the prevalence of HCV-related listed and transplanted pts from 2005 to 2016 and the improvement rate (IR).

Methods: From Jan 2005 to Dec 2016, 823 pts were consecutively listed at our center (629 – 76% – were transplanted). We identified 3 groups (G): GA-IFN age (2005–2011); GB-First Generation DAA (2012–2014) and GC-Second generation DAAs (2015–2016). Data were retrospectively analyzed.

Results: The mean prevalence of patients listed for HCV (both ESLD + HCC) in GC (43%) was lower than in the other group, although the difference was not significant (GA vs C: $p = 0.61$; GB vs C: $p = 0.06$). A decreasing number of pts listed for HCV-ESLD (GA: 36%; GB: 42%; GC: 34%) and an increase of HCV-HCC (GA: 49%; GB: 53%; GC: 54%) was observed in the last two years (p = ns). 219 pts were transplanted for HCV-related liver disease (52% for ESLD, 48% for HCC). The ratio HCV OLT/overall listed pts achieved a nadir in group C (27%), significantly lower than in GB (38%; $p = 0.008$) and GA (33%; $p = 0.06$). The ratio HCV OLT/HCV listed showed a progressive decrease with a significant difference between GC vs GA (GC – 65%; GA – 82%; $p = 0.02$) and vs GB (GB – 81%; $p = 0.03$). The IR (sum of delisted and inactivated pts) of HCV pts in the last two years was higher than in the others (GC: 27% – all DAA treated – vs GB: 7%; $p = 0.02$) vs GA (5%; $p = 0.02$).

Conclusion: Our data shows a trend toward an overall reduction of HCV prevalence in patients listed per OLT after just 2 years of DAAs. As expected a relative prevalence of HCC rather than ESLD has been shown. The IR observed in waitlist treated pts is consistent with the recent literature.

https://doi.org/10.1016/j.dld.2018.01.044

F-07

Microwave ablation and salvage transplantation for patients with hepatocellular carcinoma

A. Bertacco, A. Vitale, M. Di Giunta, E. Fasolo, M. Polacco, R. Boetto, D. Bassi, U. Cillo

Department of Surgery, Oncology and Gastroenterology, Hepatobiliary Surgery and Liver Transplantation, Padua University, Padua, Italy

Background: There are no studies evaluating a strategy based on microwave laparoscopic ablation (MLA) followed by salvage liver transplantation (LT) for HCC patients.

Methods: Between 2009 and 2016, 189 patients were treated with primary MLA, followed by transplantation in the event of a transplantable recurrence or liver failure. A similar cohort of 223 patients underwent TACE (2009–2015) as first therapy served as a control group. All patients enrolled were diagnosed as HCC within the Milan criteria, with Child A–B cirrhosis, were judged unsuitable for liver resection or percutaneous ablation and were eligible for LT. An inverse probability weights analysis was performed to match the two groups.

Results: Overall survival resulted significantly higher in patients underwent MLA ($p = 0.02$) with a median follow up of 67 months (vs 56 months in control group). 13% of patients treated with MLA needed a salvage transplant against 19% of patients underwent TACE: the difference was statistically significant ($p = 0.02$).

Conclusion: On an individual patient level a strategy based on MLA as first-line therapy for HCC patients considered unsuitable for resection or percutaneous ablation has proved to be more effective than TACE for the same patients. From a population perspective, on the other hand, this strategy enabled a significant sparing of organs for transplantation, thus affording a potentially relevant benefit in geographical areas with donor shortages or a high prevalence of HCC.

https://doi.org/10.1016/j.dld.2018.01.045

F-08

Multimodal and sequential treatment for hepatocellular carcinoma: How "real-life" complies with international recommendations

M. Triolo[1,2], A. Sangiovanni[1], M. Iavarone[1], L.V. Forzenigo[3], A. Nicolini[4], G. Rossi[5], V. La Mura[2], M. Colombo[6], P. Lampertico[1]

[1] *CRC "A.M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[2] *Division of Internal Medicine, Policlinico S. Donato, University of Milan, San Donato Milanese, Italy*
[3] *Division of Radiology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[4] *Division of Interventional Radiology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[5] *Division of Surgery and Liver Transplant, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[6] *Humanitas Clinical and Research Center, Rozzano, Italy*

Background: Management of hepatocellular carcinoma (HCC) is framed within standardized protocols released by Scientific Societies, whose applicability and efficacy in field practice need refining.

Aim: We evaluated the applicability and effectiveness of guidelines for the treatment of HCC of the American Association for the Study of the Liver (AASLD).

Methods: Between January 2007 and December 2011, 370 consecutive cirrhotic patients (median age 68 yrs, 272 males, 250 Child–Pugh A) with de-novo HCC (253 BCLC A, 66 BCLC B, 51 BCLC C) received treatment through a multidisciplinary team (MDT) decision. Patients were followed until death or last follow-up up to December 2016.

Results: HCC treatment was adherent to AASLD recommendations in 205 (81%) BCLC A patients, 36 (54%) BCLC B, and 27 (53%) BCLC C. Overall, a radiological complete response was obtained in 185 (50%) patients, 165/370 (45%) after a first-line treatment, 25/117 (21%) after a second-line treatment, and 6/39 (15%) after a third-line treatment. Eleven patients (3%) achieved a complete response more than once.

During 58 (range 1–108) months, 105 (28%) patients died, 41 (16%) BCLC A, 25 (38%) BCLC B and 39 (74%) BCLC C. In BCLC A the mean mortality rate was lower in patients treated according to AASLD recommendations than in patients otherwise treated (5.0% vs 10.4%, $p = 0.004$), whereas the upward treatment stage migration was associated to a lower mortality rate as compared to standard of treatment in BCLC B (8.6% vs 20.7%, $p = 0.029$), as well as in BCLC C (42.6% vs 59%, $p = 0.04$), respectively.

Conclusions: HCC multimodality treatment including other than first-line therapy is common in clinical practice and impacts on the achievement of complete response. Personalized treatment provided survival benefits to patients whose profile is not accounted for by international recommendations.

https://doi.org/10.1016/j.dld.2018.01.046

F-09

Temporal trends of access to DAAs treatments for HCV in the Navigatore-Lombardia network: Evolution of AIFA criteria, DAA regimens and patient features

L. Pasulo[1], A. Aghemo[2], G. Rizzardini[3], R. Rossotti[4], M. Vinci[5], A. Spinetti[6], G. Filice[7], P. Grossi[8], A. Ciaccio[9], M. Colombo[2], P. Lampertico[10], S. Fagiuoli[1], on behalf of the NAVIGATOR-L Study group[11]

[1] *Gastroenterology, ASST Papa Giovanni XXIII, Italy*
[2] *Humanitas University Department of Biomedical Sciences, Rozzano-Milan, Italy*
[3] *Infectious Diseases, Sacco Hospital, Italy*
[4] *Infectious Diseases ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[5] *Gastroenterology, Ca Granda Niguarda, Milan, Italy*
[6] *Infectious Diseases, Spedali Civili, Brescia Bergamo, Italy*
[7] *Infectious Diseases, Policlinico Pavia, Italy*
[8] *Infectious Diseases, Varese Hospital, Italy*
[9] *Hepatology, San Gerardo Hospital, Monza, Italy*
[10] *CRC "A. M. e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*

Background and aim: Since the availability of IFN-Free anti-HCV treatment several new drug regimens have progressively been utilized in clinical practice. Aim of this report is to describe the temporal switch in access to DAAs in term of AIFA criteria indications, DAA regimens of choice and features of the treated patients within the large real life-database of the Lombardia Region.

Methods: Consecutive HCV-patients starting DAA between January2015 and December2017 within the treating Centres of the

[11] L.S. Belli, R. Bruno, S. Bruno, E. Buscarini, I. Carderi, A. Ciaccio, A. Colli, G. Colloredo, A.E. Colombo, M. Colpani, A. Corbellini, A. D'Arminio Monforte, P. Del Poggio, M. Di Marco, L. Fugazza, A. Gori, P. Ghiringhelli, M. Graffeo, R. Gulminetti, P. Invernizzi, S. Lazzaroni, A. Lleo, G. Lorini, F. Maggiolo, B. Menzaghi, L. Minoli, L. Morini, B. Omazzi, A. Pan, B. Paris, G. Perboni, M.G. Pigozzi, L. Pusterla, T. Quirino, T. Re, M. Rumi, P. Sacchi, D. Somaschini, M. Soncini, A. Soria, A. Spinetti, G. Spinzi, M. Strazzabosco, P. Tau, N. Terreni, M. Tinelli, R. Turrini, C. Uberti Foppa, P. Viganò, M. Vinci, M. Zuin.

Table 1

	AIFA 1%	AIFA 2%	AIFA 3%	AIFA 4%	AIFA 5%	AIFA 6%	AIFA 7%	AIFA 8%	AIFA 9%	AIFA 10%
1° 2015	71,3	4,73	5,56	15,95	1,54	0,41	0,41			
2° 2015	76,84	4,13	3,91	13,79	0,81	0,37	0,15			
3° 2015	67,3	5,59	5,83	19,68	0,54	0,42	0,65			
1° 2016	59,52	5,17	7,19	26,17	0,57	0,44	0,95			
2° 2016	55,69	2,63	8,01	32,17	0,38	0,5	0,63			
3° 2016	45,84	3,09	9,7	39,13	0,21	0,75	1,07			
1° 2017	43,56	3,92	9,3	40,29	0,49	1,63	0,49			
2° 2017	21,62	2,25	4,28	18,47	0,45	1,13	25,45	23,42	2,03	0,9
3° 2017	22,8	1,16	3,49	9.0	0	0,57	26,16	36,63	0	0

Table 2

	LED+SOF%	3D %	DAC+SOF%	SOF+RBV%	SIM+SOF%	SOF*VEL%	ELB+GRZ%	PEG+DAA%	G/P%	Others%
1° 2015	0,84	6,36	5,14	40,22	44,15	0	-	2,81	-	0,37
2° 2015	27,7	15,96	23,9	8,72	23,6	0,14	0,07	0,42	-	0,07
3° 2015	39,37	31,97	14,14	11,4	2,65	-	0,06	0,66	-	0,11
1° 2016	42,71	24,6	16,81	12,48	2,23	-	-	1,17	-	0
2° 2016	43,26	22,34	20,8	11,11	1,77	-	-	0,71	-	0
3° 2016	38,56	22,79	27,6	8,65	0,77	-	-	0,96	-	0,67
1° 2017	32,88	19,81	33,29	2,56	0	0,13	10,38	0,81	-	
2° 2017	7,42	27,15	9,77	0,59	0,39	25,59	27,15	0,2	-	1,76
3° 2017	1,08	25,41	2,16	0	0,54	51,89	15,68	0	3,34	0

Network have been included. The temporal trend has been analysed dividing the treating periods in 4-months blocks.

Results: 9334 patients are included in the analysis: the temporal trend of the AIFA-criteria is shown (Table 1).

The trend in DAA-regimens choice is reported (Table 2):

During the enrolment period there was a switch in HCV genotype distribution. HCV-1 remained the most prevalent (1° 2015 52.6%–3° 2017 50.2%), while there was an increase in HCV-2 prevalence (1° 2015 18.1%–3° 2017 31.9%) and a decrease in HCV-3 prevalence (1° 2015 19.6%–3° 2017 9.7%). The mean (60.7 ± 10.4 yrs) and median (59.0: 53.1–69.5 yrs) ± age in the first quarter is significantly lower than the mean (61.7 ± 15.0) and median (64.4: 51.7–75.4) observed in the 3rd quarter of 2017 ($p = 0.0001$).

The mean (8.9 ± 3.2) and median (8.0: 7.0–10.0) MELD-score in the first quarter is significantly greater than the mean (7.2 ± 3.1) and median (7.0: 6.0–8.0) score observed in the 3rd quarter of 2017.

The SVR has progressively increased across all genotypes moving from the initial access until the recent access: overall mean SVR 89.8% in 1st quarter of 2015, compared with 98.7 and 100.0% in 1st and 2nd quarter of 2017.

Conclusions: The access to DAA-based treatments for HCV, due to the rapid and progressive availability of new and effective drug combinations, is undergoing a significant switch in terms of severity of the treated diseases, genotypes, age of patients maintaining an extraordinary success rate

https://doi.org/10.1016/j.dld.2018.01.047

F-10

Characterization of resistance profiles in HCV 2-3-4 DAA-naïve and DAA-experienced infected patients in Italy

S. Barbaliscia[1], V.C. Di Maio[1], E. Teti[2], I. Lenci[3], M. Aragri[1], E. Polilli[4], G. Fiorentino[5], V. Pace Palitti[6], B. Bruzzone[7], S. Paolucci[8], N. Coppola[9], T. Ruggiero[10], T. Pollicino[11], F. Niero[12], V. Micheli[13], L.A. Nicolini[14], S. Marenco[15], A. Bertoli[1], I. Maida[16], S. Francioso[3], L. Foroghi[2], V. Calvaruso[17], F. Morisco[18], A. Lleo[19], V. Boccaccio[19], A. Ciancio[20], R. Maserati[21], M. Puoti[22], M. Zazzi[23], B. Rossetti[24], V. Vullo[25], A.R. D'Ambrosio[26], L. Boglione[27], S. Bonora[27], S. Babudieri[16], G. Gubertini[12], M. Rendina[28], A. Pellicelli[29], V. Sangiovanni[30], A. Ciaccio[31], G. Taliani[32], G. Raimondo[11], G.B. Gaeta[9], A. Craxì[17], C. Pasquazzi[5], L. Sarmati[2], G. Parruti[4], M. Angelico[3], M. Andreoni[2], V. Cento[1], C.F. Perno[33], F. Ceccherini-Silberstein[1], on behalf of HCV Virology Italian Resistance Network (Vironet C)

[1] *Department of Experimental Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy*
[2] *Infectious Diseases, University Hospital of Rome Tor Vergata, Rome, Italy*
[3] *Hepatology Unit, University Hospital of Rome Tor Vergata, Rome, Italy*
[4] *Infectious Disease Unit, Pescara General Hospital, Pescara, Italy*
[5] *Infectious Diseases, Sant'Andrea Hospital – "La Sapienza" University, Rome, Italy*
[6] *Hepatology Unit, Pescara General Hospital, Pescara, Italy*
[7] *Hygiene Unit, IRCCS AOU San Martino-IST, Genoa, Italy*
[8] *Molecular Virology, IRCCS Policlinic Foundation San Matteo, Pavia, Italy*
[9] *Infectious Diseases and Viral Hepatitis Unit, Second University of Naples, Naples, Italy*

[10] *Laboratory of Microbiology and Virology, Amedeo di Savoia Hospital, ASL Città di Torino, Turin, Italy*
[11] *Department of Internal Medicine, University Hospital of Messina, Messina, Italy*
[12] *Division of Infectious Disease, ASST Fatebenefratelli Sacco, Milan, Italy*
[13] *Clinical Microbiology, Virology and Bioemergencies, ASST Fatebenefratelli Sacco, Milan, Italy*
[14] *Infectious Disease, IRCCS AOU San Martino – IST, Genova, Italy*
[15] *Hepatology, IRCCS AOU San Martino – IST, Genova, Italy*
[16] *Infectious Diseases Unit, University of Sassari, Sassari, Italy*
[17] *Gastroenterology, "P. Giaccone" University Hospital, Palermo, Italy*
[18] *Department of Clinical Medicine and Surgery, University "Federico II" of Naples, Naples, Italy*
[19] *Department of Biomedical Sciences and Humanitas Clinical and Research Center, Humanitas University, Rozzano, Milan, Italy*
[20] *Unit of Gastroenterology, University of Turin, Department of Medical Sciences, City of Health and Science of Molinette Turin Hospital, Turin, Italy*
[21] *Institute of Infectious Diseases, University of Pavia, Pavia, Italy*
[22] *Department of Infectious Diseases, Hospital Niguarda Ca'Granda, Milan, Italy*
[23] *Virology, Siena University Hospital, Siena, Italy*
[24] *Infectious Diseases, Siena University Hospital, Siena, Italy*
[25] *Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy*
[26] *Unit of Gastroenterology and Hepatology, IRCCS Foundation "Ca' Granda-Ospedale Maggiore Policlinico", Milan, Italy*
[27] *Unit of Infectious Diseases, Department of Medical Sciences, Amedeo di Savoia Hospital, University of Turin, Turin, Italy*
[28] *Department of Emergency and Organ Transplantation, Section of Gastroenterology, University Hospital, Bari, Italy*
[29] *Hepatology Unit, San Camillo Forlanini Hospital, Rome, Italy*
[30] *Hospital Cotugno, Naples, Italy*
[31] *Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy*
[32] *Infectious and Tropical Diseases Unit, Department of Clinical Medicine, "La Sapienza" University of Rome, Rome, Italy*
[33] *University of Milan, Milan, Italy*

Background and aims: Pan-genotypic direct-acting antivirals (DAA) will be the most used regimens. However, their use, in short, ribavirin-free regimens may be affected by the presence of resistance-associated-substitutions (RASs), whose prevalence varies within HCV-genotypes (GTs). This study investigated the resistance profile in HCV 2-3-4 infected, DAA-naïve and DAA-experienced, Italian patients.

Method: GT2-3-4 (N = 109/289/121) infected patients, DAA-naïve or DAA-experienced (N = 419/116) were included. Sanger-sequencing of NS3 ± NS5A ± NS5B was performed by home-made protocols.

Results: Phylogenetic analysis identified different HCV-subtypes: GT2c (100%), GT3a/h (99.3%/0.7%), GT4a/d (11.6%/88.4%). Overall, 16.0% of DAA-naïve and 83.6% of DAA-failures had at least 1 RAS ($p < 0.001$). Notably, 11.2% of patients were treated with a sub-optimal DAA-regimen due to a previous incorrect GT assignment and harbored RASs in 92.3% of cases.

NS3-Q80 K was mainly detected in GT3a paritaprevir-failures (25%, vs 1% in DAA-naïves, $p = 0.007$). NS3-D168 V was detected in 66.7% GT2c and 100% GT4d paritaprevir-failures, and in 45.4% GT4d simeprevir failures, while was rarely observed in DAA-naïve GT2c and GT4d patients (0.0% and 2.6%, respectively). The NS5A-Y93H was prevalent in NS5A-experienced GT3a (78.9%), GT4a (25%) and GT4d (14.3%) patients while it was rarely detected in DAA-naïves (3.9% in GT3a, <2% in GT4a/d). No patients with GT2c infection showed the NS5A-Y93H, while NS5A-F28C was detected in 71.4% GT2c NS5A-failures and in 27.8% GT2c DAA-naïves ($p = 0.03$). The S282T sofosbuvir-RAS was found only in sofosbuvir-containing regimen-failures, rarely in GT4d 3.3% and GT3a 4.4%, while was frequently detected 75% in GT4a ($p = 0.001$).

Notably, of the 75 GT3 DAA-naïve patients treated with daclatasvir + sofosbuvir + ribavirin for 12–24 w, 89.3% reached SVR. 2/4 (50.0%) patients with baseline NS5A-Y93H reached SVR vs 63/68 (92.6%) without NS5A-RAS ($p = 0.04$).

Conclusion: HCV-sequencing allows correct GT assignment and evaluation of resistance in all GTs. Failure is frequently associated with RASs, particularly Y93H-NS5A in GT3a, F28C-NS5A in GT2c and S282T-NS5B in GT4a, with potential impact on retreatment efficacy.

https://doi.org/10.1016/j.dld.2018.01.048

F-11

The protease-inhibitor SerpinB3 outlines a stem-like subset in human cholangiocarcinoma

C. Raggi[1], A. Cappon[2], M. Correnti[3], J.B. Andersen[4], E. Forti[3], G. Cavalloni[5], E. Torchio[6], P. Pontisso[2], F. Marra[1]

[1] *Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze, Florence, Italy*
[2] *Department of Medicine (DIMED), University of Padova, Padova, Italy*
[3] *Center for Autoimmune Liver Diseases, Humanitas Clinical and Research Center, Rozzano, Italy*
[4] *Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark*
[5] *Medical Oncology Division, Fondazione del Piemonte per l'Oncologia (FPO), IRCCS-Institute Candiolo, Italy*
[6] *Dipartimento Ingegneria Industriale, University of Padova, Padova, Italy*

Background and aims: Cholangiocarcinoma (CCA) is a severe adenocarcinoma of biliary epithelial cells. Along with hepatocellular carcinoma (HCC), CCA represents the major primitive liver cancer. Recently, cancer stem cells (CSCs) have been proposed as a driving force of tumor initiation, dissemination and drug resistance thus representing a primary therapeutic target. Protease inhibitor SerpinB3 has been identified in several malignancies including HCC. Although almost undetectable in normal hepatocytes SerpinB3 is progressively up-regulated in liver cirrhosis, dysplastic nodules and HCC, suggesting its role in hepatocarcinogenesis early events. Furthermore, SerpinB3 is highly expressed in hepatic EpCAM+ progenitor cells as well as in a mouse model of liver stem/progenitor cell activation. Thus, present study aimed to evaluate SerpinB3 regulatory function in CCA stem-pool.

Methods: Enrichment of CCA stem-like subset was performed by sphere culture (SPH) in both established (HUCCT1) and primary (MTCHO1) cells. Detection of SPH-SerpinB3 by both qRT-PCR and ELISA of cultured medium. SerpinB3 evaluation in human CCA sections by immunohistochemistry (IHC). Overall survival (OS) (log rank/Mantel-cox statistics) and time to recurrence (TTR) (Gehan–Breslow Wilcoxon test) analysis carried out from transcriptome database of 104 CCA patients.

Results: SerpinB3 enhanced expression and release was revealed in CCA-SPH compared to parental cells monolayers (MON). Notably, 6-day-MON-treatment with 150 ng/ml recombinant SerpinB3 showed significant overexpression of CSC-like (CD44, CD133), pluripotency (SOX2, NANOG, OCT4), stem-signaling (STAT3, NOTCH1) and drug-resistance (ABCG2) genes, suggesting its possible contribution to CCA-stem subset. SerpinB3-transfected MON showed superior invasion capacity compared to controls. Furthermore, SerpinB3 overexpression was observed in human CCA tissues and Kaplan Mayer curves for both OS and TTR indicated a clear worse prognosis for SerpinB3^{+} CCA patients.

Conclusion: These findings provide new insights of SerpinB3 supportive role of CCA initiation thus suggesting an alternative therapeutic target.

https://doi.org/10.1016/j.dld.2018.01.049

F-12

Liver stiffness predicts the development of portal hypertension related complications in advanced chronic liver disease

L. Mulazzani [1], V. Sansone [1], A. Berzigotti [2,3], H. Stefanescu [1,4], G. Allegretti [1], F. Ravaioli [1], G. Marasco [1], C. Di Bonaventura [1], C. Serra [1], R. Vukotic [1], L. Bolondi [1], J. Bosch [3], F. Piscaglia [1], on behalf of the CLEVER Study investigators

[1] *Department of Medical and Surgical Sciences, University of Bologna, Italy*
[2] *Hepatology, Inselspital, University of Bern, Switzerland*
[3] *Liver Unit, Hospital Clínic-IDIBAPS, University of Barcelona, Spain*
[4] *Hepatology Unit, Regional Institute of Gastroenterology and Hepatology, Cluj Napoca, Romania*

Introduction: Shear wave elastography (SWE) is a promising tool to grade the severity of advanced chronic liver disease (CLD) but its prognostic capacity to predict the future occurrence of portal hypertensive complications has not been validated yet. The latter is particularly true in the instance of HCV patients achieving SVR, where prognostic predictors are lacking.

Aim: To assess the role of liver stiffness (LS) compared with other clinical and laboratory variables in predicting the occurrence of complications in patients with stage F≥3 CLD.

Methods: Data were collected within the prospective EC-funded CLEVER study (FP7-IAPP-GA-2013-612273-CLEVER) aimed at identifying new tools for prognosis prediction in advanced CLD. Of 137 CLD patients (mean age 61.3 ± 11.1 years) with fibrosis ≥F3 submitted to SWE (with either 2DSWE SuperSonic Imagine or transient elastography with Fibroscan) 99 with no previous decompensation were enrolled.

Results: Etiology: 64 HCV (44 treated with direct antiviral agents before or after enrolment, 43 achieving SVR), 7 HBV, 4 alcohol, 24 other. Mean follow-up: 21.4 ± 10.5 months. First decompensation of CLD occurred in 6 patients (4 ascites, 1 encephalopathy, 1 bleeding), of which 4 were HCV+ (3 SVR, 1 untreated). Decompensating patients showed higher median LS (39.3, IQR 29.2 vs 14.4, IQR 10.4 kPa; $p < 0.001$) and MELD scores (10, IQR 2 vs 8, IQR 2; $p = 0.01$) at baseline. All decompensating patients had LS >20 kPa at inclusion, compared to only one third of the others. Cox proportional hazard regression identified only LS as independent predictor of decompensation, with a Hazard Ratio of 1.075 (1.038–1.113, $p < 0.001$). MELD score, platelet count, esophageal varices and spleen diameter were not independent predictors of complications.

Conclusion: Liver stiffness measured by SWE predicts the development of complications in advanced CLD. LS >20 kPa identifies a group of patients at higher risk of developing clinical decompensation.

https://doi.org/10.1016/j.dld.2018.01.050

F-13

Insulin resistance improvement after effective Hepatitis C virus eradication and its role on the onset of complications of advanced liver disease

I. Bortoluzzi [1], E. Franceschet [1], M. Gambato [2], A. Zanetto [1], A. Ferrarese [1], S.S. Sciarrone [1], F. Farinati [1], P. Burra [2], A. Mega [3], F.P. Russo [1,2]

[1] *Gastoenterology, Department of Surgery, Oncology and Gastroenterology, University Hospital Padua, Italy*
[2] *Multivisceral Trnsplant Unit, Department of Surgery, Oncology and Gastroenterology, University Hospital Padua, Italy*
[3] *Gastroenterology Unit, Bolzano Hospital, Italy*

Background: Insulin resistance (IR) is a common extrahepatic manifestation of Hepatitis C virus (HCV) infection. Few data are available about the relationship between IR and the new direct-acting antiviral (DAA) drugs.

Aim: To evaluate if viral eradication obtained with DAA allows improvement of IR; furthermore, we evaluate if IR improvement reduces hepatic complications incidence.

Methods: We evaluated all HCV patients treated with DAA from May 2015 to December 2016 2 referral Centre. For each patient, we analyzed blood test and HOMA score before therapy and 3, 6 and 12 months after its completion, liver fibrosis with transient elastography before therapy, 6 and 12 months after the end of treatment (EOT). IR has been defined as HOMA score ≥2.5.

Results: Among the 161 patients included in the study 117/161 (72.7%) had IR and 44/161 (27.3%) not. Patients with IR had higher BMI (p 0.0094) and liver fibrosis ($p < 0.0001$) levels compared to those without IR. 158/161 (98.1%) patients obtained viral eradication. We observed a significant IR improvement both 6 months (p 0.0412) and 12 months (p 0.0045) after therapy completion; 4 diabetic patients obtained resolution of diabetes. High BMI before antiviral therapy was the only variable related to the failed improvement of IR. All patients obtained significant liver fibrosis reduction after DAA therapy ($p < 0.0001$), significant improvement in serum albumin levels and platelets count and transaminases normalization. 8/161 (3.9%) patients had a diagnosis of hepatocellular carcinoma (HCC) during follow up (4/8 de novo HCC, 4/8 HCC recurrence); 7/8 of these patients had IR.

Conclusions: Viral eradication with DAA leads to IR improvement. High BMI is a risk factor for IR development and a negative predictive factor for IR improvement. Persistence of IR after DAA therapy is a risk factor for liver disease complications, such as HCC.

https://doi.org/10.1016/j.dld.2018.01.051

F-14

Early treatment with sorafenib and mTOR inhibitor in recurrent hepatocellular carcinoma after liver transplantation: Safety and survival

F. Invernizzi [1], M. Iavarone [1], M.F. Donato [1], A. Sangiovanni [1], S. Monico [1], M.A. Manini [1], U. Maggi [2], B. Antonelli [2], D. Dondossola [2], G. Rossi [2], P. Lampertico [1]

[1] *A.M. & A. Migliavacca Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Maggiore Hospital, University of Milan, Italy*
[2] *HBP Surgery and Liver Transplantation Unit, Fondazione IRCCS Ca' Granda Maggiore Hospital, University of Milan, Italy*

Background and aims: Sorafenib is currently used in hepatocellular carcinoma (HCC) recurring after liver transplantation (LT), generally when other approaches are unsuitable, while the association of sorafenib and mTOR inhibitors (mTORi) has been poorly studied. Aim of the study was to assess the safety and effectiveness of early introduction of sorafenib + mTORi for HCC recurring after LT.

Methods: Patients with HCC recurring after LT started sorafenib + mTORi in a longitudinal cohort study. Surgical/locoregional treatments were performed before and during sorafenib + mTORi. Modifications and interruptions of sorafenib and mTORi were based on adverse events (AE), liver graft dysfunction and/or symptomatic cancer progression. Endpoints were safety, effectiveness and overall survival (OS).

Results: Twenty non-cirrhotic patients received sorafenib + mTORi as soon as HCC recurred (age 58, male 80%, HCV-RNA positive 20%, surgery/locoregional treatments 75%). During 12 (1–70) months of sorafenib treatment all patients had at least one sorafenib-associated AE, generally graded 1–2. Sorafenib was reduced in 15 patients and discontinued in 9 (symptomatic progression in 6, AE in one, liver graft dysfunction in 2). mTORi-associated AEs occurred in 9 patients, dose was reduced in 6 and discontinued in 4. No significant drug-drug interactions were registered. Time-to-first radiological progression was 7.5 months (95%CI 3.9–11). Eight patients died, all for HCC progression: the 1- and 5-year cumulative OS were 82% (95%CI 53–94%) and 33% (95%CI 9–61%), respectively, with a median OS of 29 months (95%CI 26–31).

Conclusion: Early treatment with sorafenib + mTORi combined with locoregional treatments extended patients' survival with a favourable safety profile in HCC recurring after LT.

https://doi.org/10.1016/j.dld.2018.01.052

F-15

Changes of AFP and PIVKA-II levels during DAA treatment and their predictive value for early diagnosis of HCC in HCV cirrhotic patients with SVR to DAA treatment

A. Sangiovanni [1], R. D'Ambrosio [1], G. Lunghi [2], M. Bruccoleri [1], E. Alimenti [1], M. Borghi [1], R. Perbellini [1], A. Aghemo [3], M. Iavarone [1], M. Colombo [3], P. Lampertico [1]

[1] *CRC "Centro A.M. e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico – University of Milan, Milano, MI, Italy*
[2] *Virology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico – University of Milan, Milano, Italy*
[3] *Center for Translational Hepatology Research, Humanitas Research Hospital, Rozzano, Italy*

Introduction: Scanty data are available on performance of tumor markers in HCV patients with sustained virological response (SVR) to direct antiviral agents (DAA) treatment. Aim of this study was to define the changes of serum values of AFP and PIVKA-II after DAA treatment and their diagnostic performance for the diagnosis of HCC in HCV cirrhotic patients with SVR.

Material and methods: This single center case–control study evaluates AFP and PIVKA-II at DAA starting and at SVR in 90 cirrhotic patients with no history of HCC and no evidence of development of HCC during a median follow up of 16 (5–27) months (Group 1) and at HCC diagnosis in 30 patients with SVR to DAA therapy (Group 2). Patients were matched 3:1 for age (66 years), sex (76% males), and BMI (24.91). AFP = 20 ng/mL and PIVKA-II = 80 mAU/mL were used ad a cutoff for calculating sensitivity, specificity, PPV, NPV and diagnostic accuracy of tumor markers.

Results: In Group 1 median values fell from 14 ng/mL at DAA starting to 6 ng/mL at SVR 12 ($p < 0.001$), while PIVKA-II remained unchanged (36 vs. 35 mAU/mL, $p = 0.71$). AFP and PIVKA-II at SVR were significantly lower in cirrhotic patients than in HCC patients (6 vs. 10 ng/mL, $p = 0.0005$; 35 vs. 64.5 mAU/mL, $p < 0.001$, respectively). Sensitivity of AFP and PIVKA-II at SVR were 25%, 47%, respectively, specificity 98%, 91%, respectively, PPV 80% and 64%, NPV 80% and 84%, diagnostic accuracy 80%, 80%, respectively. Combining tumor markers, specificity improved to 100% with sensitivity, PPV, NPV and diagnostic accuracy of 17%, 100%, 78% and 79% respectively.

Conclusions: AFP but not PIVKA-II values significantly decreased at SVR in HCV cirrhotic patients without HCC treated with DAA treatment. The combination of AFP and PIVKA-II achieves absolute specificity for the diagnosis of HCC in SVR patients.

https://doi.org/10.1016/j.dld.2018.01.053

F-16

HCC recurrence after DAA treatment in HCV patients

M. Guarino[1], D. Bruzzese[2], G.G. Di Costanzo[3], M. Guarracino[3], F. Morando[1], L. Rinaldi[4], M. Persico[5], A. Salomone Megna[6], N. Coppola[7], N. Caporaso[1], F. Morisco[1]

[1] *Gastroenterology Unit, Department of Clinical Medicine and Surgery, University of Naples "Federico II", Naples, Italy*
[2] *Department of Public Health, University of Naples "Federico II", Naples, Italy*
[3] *Hepatology Unit, "Cardarelli" Hospital, Naples, Italy*
[4] *Department of Medical, Surgical, Neurological, Geriatric and Metabolic Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy*
[5] *Department of Medicine and Surgery, University of Salerno, Salerno, Italy*
[6] *Division of Infectious Diseases, Rummo Hospital, Benevento, Italy*
[7] *Department of Mental Health and Public Medicine, Section of Infectious Diseases, University of Campania "Luigi Vanvitelli", Naples, Italy*

Background/aim: Several studies reported conflicting data about the possible increased risk of HCC recurrence after DAAs therapy. The present real-life multicenter prospective study aims to investigate the impact of new IFN-free therapies in HCV patients with a previous HCC, in terms of neoplastic recurrence.

Methods: From March 2015 to March 2017, all consecutive HCV patients with a previous successfully treated HCC underwent DAAs therapy were enrolled. The baseline clinical, biochemical and radiological data were registered. The assessment of neoplastic recurrence was used as primary outcome, while a secondary outcome was the evaluation of patients characteristics predicting HCC recurrence.

Results: Eighty patients (mean age 66.8 ± 8.19 yrs, 63.8% male, BMI 25.8 ± 3.01) were consecutively enrolled. Eighty-two percent of them were in Child–Pugh class A, and 86% had a history of HCC BCLC stage 0/A, while 36.3% of patients had a prior HCC recurrence. Eighty-eight percent of the patients achieved sustained virological response (SVR). The median time between the last HCC treatment and DAAs-starting was 10.2 months (range 4.8–18.2), while the median time from the radiological confirmation of HCC complete response was 4.8 (range 2.3–11.5) Twenty-two HCC recurrences were observed from DAA-starting in a median observational follow-up of 15.9 months (range 10.5–23.5), showing a nodular or infiltrative pattern in 91% and 9%, respectively. The cumulative rate of recurrence was 19.6/100 person-year (95%C.I. 12.3–29.7). The 6-, 12- and 24-month HCC recurrence rates were 11.2%, 19.1% and 30.1%, respectively. Higher BMI (HR 1.25, 95%C.I. 1.06–1.48) and DAAs treatment failure (5.43, 95%C.I. 1.84–16.05) were significantly associated with higher risk of HCC recurrence, both at univariate and at Cox multivariate analysis.

Conclusions: Patients without HCC recurrence are characterized by lower BMI and higher SVR rate. These data suggest that the absence of well-known HCC risk factors reduces the recurrence rate of HCC also in patients treated with DAAs.

https://doi.org/10.1016/j.dld.2018.01.054

F-17

Immune inflammation indicators and ALBI score to predict occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals

A.C. Gardini[1], F.G. Foschi[2], F. Conti[3], E. Petracci[4], G. Marisi[5], F. Buonfiglioli[3], M. Ravaioli[3], G. Mazzella[6], P. Muratori[7], M. Lenzi[7], C. Crespi[8], L. Bolondi[6], L. Badia[9], G. Verucchi[3], G. Vitale[3], R. Vukotic[3], S. Brillanti[3], P. Andreone[3]

[1] *Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e Cura dei Tumori (IRST) IRCCS, Meldola, Italy*
[2] *DPT Internal Medicine, Faenza Hospital, Faenza, AUSL Romagna, Forli, Italy*
[3] *Research Centre for the Study of Hepatitis, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy*
[4] *Unit of Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy*
[5] *Biosciences Laboratory, IRST IRCCS, Meldola, Italy*
[6] *Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy*
[7] *Center for the Study and Treatment of Autoimmune Diseases of the Liver and Biliary System, Policlinico di Sant'Orsola, Bologna, Italy; Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Bologna, Italy*
[8] *Department of Digestive Diseases, Policlinico S.Orsola-Malpighi, Bologna, Italy*
[9] *Infectious Diseases Unit, Department of Medical and Surgical Sciences, Hospital S. Orsola-Malpighi, University of Bologna, Italy*

Introduction: Recent studies have shown unexpected high HCC recurrence rate of 27–29% among patients treated with resection or ablation, who received DAA therapy, but this results were not reproduced in others analyses.

Aim: The aim of this study was to evaluate the prognostic value for occurrence and recurrence of hepatocellualr carcinoma of ALBI grade and immunoinflammation indicators [systemic immune-inflammation index (SII); platelet to lymphocyte ratio (PLR); AST to lymphocyte ratio index (ALRI)] in patients treated with DAA for chronic hepatitis C.

Materials and methods results: In this retrospective cohort study, we analysed data from all the consecutive patients with cirrhosis who were prospectively enrolled for treatment with DAAs. We analysed the basal level of NLR, SII, PLR, ALRI and ALBI.

For patients without history of previous HCC (416 patients) we analysed the clinical characteristics and the risk of HCC development. Based on univariate analysis, increase of AST ($p = 0.036$, HR: 1.01, 95%CI: 1.00–1.01), increase of bilirubin ($p = 0.035$, HR: 1.46, 95%CI: 1.03–2.08), decrease of albumin ($p = 0.004$, HR: 0.34, 95%CI: 0.17–0.71), increase ALRI score ($p = 0.002$, HR: 1.01, 95%CI: 1.0–1.01) decrease of platelets ($p = 0.007$, HR: 0.99, 95%CI: 0.98–1.00) and increase of ALBI grade ($p = 0.001$, HR: 2.99, 95%CI: 1.45–6.15) were associated with HCC development.

At multivariate analysis, two variables resulted independently associated with HCC development: increase of ALBI grade ($p = 0.038$, HR: 2.35, 95%CI: 1.05–5.25) and decrease of platelets ($p = 0.048$, HR: 0.99, 95%CI: 0.98–1.0). We also evaluated changes in clinical parameters between baseline and the end of treatment. At baseline, patients without previous HCC had a higher

number of neutrophils and lymphocytes than those patients who had previous HCC (neutrophils: 2.96×10^9/L ± 1.33 and 2.59×10^9/L ± 1.10 respectively; lymphocytes: 1.70×10^9/L ± 0.85 and 1.37×10^9/L ± 0.77 respectively).

Conclusion: Low cost, easy determination, and reproducibility of a full blood count make ALBI grade, platelets and ALRI a promising tool for evaluate patients with high risk of hepatocellular carcinoma after treatment with direct-acting antiviral.

https://doi.org/10.1016/j.dld.2018.01.055

F-18

Baseline clinical features but not TLL1 variants predicts HCC onset in Caucasian compensated HBV cirrhotics treated by Entecavir or Tenofovir for 8 years

A. Loglio [1], E. Galmozzi [1], M. Iavarone [1], G. Grossi [1], M. Viganò [2], F. Facchetti [1], R. Perbellini [1], M.G. Rumi [2], A. Sangiovanni [1], P. Lampertico [1]

[1] *CRC "A. M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy*
[2] *Division of Hepatology, Ospedale San Giuseppe, Università degli Studi di Milano, Milan, Italy*

Background and aims: As HCC remains the leading complication in HBV compensated cirrhotics long-term TDF/ETV treated, we aimed to define baseline predictors of HCC, including the tolloid like 1 gene (*TLL1*) rs17047200 polymorphism which predicts HCC in HCV patients cured by IFN therapy.

Methods: 258 Caucasian HBV-monoinfected HCC-free CPT-A cirrhotics starting TDF/ETV were consecutively enrolled in a longitudinal cohort study: 61 years, 82% males, 69% normal ALT, 12% diabetics, 60% NUCs-experienced, 5% with previously-treated HCCs, PLT 153 (48–304) $\times 10^9$/L, spleen diameter 11 (7–20) cm, liver stiffness 9 (3–60) kPa, 14% with esophageal varices (EV), LSPS 0.62 (0.12–7.57), 14% PAGE-B score ≥18. Blood tests and 6-month abdominal imaging were performed until HCC development or Nov 2017.

Results: Over 102 (18–126) months, 36 (14%) patients developed an HCC after 52 (18–100) months, with an 8-year cumulative incidence of 15%. HCC developed in 10 (15%) out of 66 AT/TT *TLL1* (26%) patients compared to 26 (13.5%) among 192 AA (74%) subjects, with a 5-year cumulative HCC incidence of 13.5% vs 8.8% ($p = 0.642$). At univariate analysis, EV presence, HCC history, spleen diameter, baseline LS, PLT count, age, LSPS and PAGE-B score predicted HCC. At multivariate analysis, previous HCC (HR 7.5), EV (HR 3.3), diabetes (HR 2.4), age (HR 1.1) and PLT (HR 0.99) predicted HCC. Among 244 patients without previous HCC, independent predictors of HCC were baseline EV (HR 3.6), spleen diameter (HR 1.6) and age (HR 1.3). The 8-year cumulative incidence of HCC was 43% and 7% among patients with or without baseline EV ($p < 0.001$), 20% and 9% in those with spleen diameter > or ≤12 cm ($p = 0.02$), and 17% *vs* 6% in those with age > or ≤60 years ($p = 0.007$).

Conclusions: Baseline portal hypertension and age strongly predict HCC, independently from *TLL1*, in HBV NUC-treated cirrhotics.

https://doi.org/10.1016/j.dld.2018.01.056

F-19

Liver stiffness based model (LSPS) predicts measured portal hypertension (mPH), esophageal varices (EVs) and HCC in patients treated and responsive to DAA for HBV and HCV-related cirrhosis

A. Tucci, W. Debernardi Venon, M. Pelizza, C. Chialà, A. Ciancio, A. Smedile, G. Saracco, A. Marzano

Department of Gastroenterology and Hepatology, San Giovanni Battista Hospital, Città della Salute e della Scienza, University of Turin, Italy

Introduction and aims: LSPS has been correlated with mPH, EV and risk of HCC in cirrhotic patients. The response to antiviral therapy with DAA reduces but does not eliminate the risk of HCC in HBV and HCV-related cirrhosis. The impact of SVR on mPH, clinical outcome and endoscopic monitoring of EVs, can be evaluated with LSPS.

Methods: Data are presented from an ongoing longitudinal study, currently performed in 236 cirrhotic patients (115 HCV positive and 121 HBV positive) responsive to antiviral therapy. They underwent LSPS measurement before therapy and LSPS + HVPG measurement + gastroscopy after SVR 6 off-therapy in HCV and complete virological response (VR) from at least 12 months on-therapy in HBV.

Results: LSPS <0.6 and <1.2 identified patients without CSPH (HVPG <10 mmHg; PPV 50%, NPV 100%) and without EVs (PPV 71%, NPV 96%), respectively. Patients who did not reach LSPS <0.93 post SVR or VR were more likely to have appearance, persistence or progression of EVs (PPV 36%, NPV 97%). HCC developed in 29/236 (12%) of the patients, 3 with HCV infection and 26 with HBV infection and a longer follow-up. LSPS ≤0.6 baseline or inducted by antiviral therapy was associated with a lower risk of HCC (NPV 98%).

Conclusions: LSPS is a useful non-invasive tool to exclude the presence of CSPH and EVs and to predict clinical outcome, avoiding unnecessary endoscopy and too frequent ultrasound. The impact of DAA therapy on HCC in HBV and HCV cirrhotic patient remains debated and requires a longer follow-up. LSPS ≤0.6 could identify a low risk group in cirrhotic patients responsive to antiviral therapy.

https://doi.org/10.1016/j.dld.2018.01.057

F-20

Evolution of HCV treatments with direct acting antivirals between 2014 and 2017 in 8637 HCV patients in a real world setting: A report from the Lombardia Network and Navigator Study Group

E. Degasperi[1], L. Pasulo[2], A. Aghemo[3], M. Puoti[4], S. Zaltron[5], F. Maggiolo[6], G. Rizzardini[7], S. Fargion[8], P. Sacchi[9], R. Gulminetti[9], M. Zuin[10], T. Quirino[11], M.G. Rumi[12], A. Pan[13], P. Grossi[14], A. Rossini[15], A. Corbellini[16], C. Uberti Foppa[17], A. Colli[18], S. Piovesan[19], P. Angeli[20], L. Chemello[20], F.P. Russo[21], P. Burra[21], V. Vincenzi[22], A.M. Cattelan[23], G. Carolo[24], F. Capra[24], G. Carlotto[25], P.A. Rovere[26], S. Lobello[27], P. Scotton[28], S. Panese[29], P. Fabris[30], A. Alberti[19], P. Lampertico[1], S. Fagiuoli[2], on behalf of the NAVIGATOR study group

[1] *CRC "A. M. e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[2] *Gastroenterology, ASST Papa Giovanni XXIII, Italy*
[3] *Humanitas University Department of Biomedical Sciences, Rozzano-Milan, Italy*
[4] *Infectious Diseases ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[5] *Infectious Diseases, Spedali Civili, Brescia Bergamo, Italy*
[6] *Infectious Diseases, ASST Papa Giovanni XXIII, Bergamo, Italy*
[7] *Infectious Diseases, Sacco Hospital, Italy*
[8] *Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[9] *Infectious Diseases, Policlinico Pavia, Italy*
[10] *Gastroenterology, San Paolo Hospital, Milan, Italy*
[11] *Infectious Diseases, Busto Arsizio Hospital, Varese, Italy*
[12] *Hepatology, San Giuseppe Hospital, Milan, Italy*
[13] *Infectious Diseases Cremona Hospital, Italy*
[14] *Infectious Diseases Varese Hospital, Italy*
[15] *Hepatology, Spedali Civili, Brescia Bergamo, Italy*
[16] *Infectious Diseases Vizzolo Predabissi Hospital, Italy*
[17] *Immunology and Infectious Diseases, San Raffaele Hospital, Milan, Italy*
[18] *Internal Medicine, Lecco Hospital, Lecco, Italy*
[19] *DMM, University of Padova, Padova, Italy*
[20] *Clinica Medica 5, University of Padova, Padova, Italy*
[21] *Dipartimento di Scienze Chirurgiche, Oncologiche e Gastroenterologiche (DiSCOG), University of Padova, Padova, Italy*
[22] *Ospedale Belluno, Belluno, Italy*
[23] *Azienda Ospedaliera di Padova, Padova, Italy*
[24] *University of Verona, Verona, Italy*
[25] *Ospedale Santorso, Vicenza, Italy*
[26] *Ospedale Legnago, Verona, Italy*
[27] *Ospedale S Antonio-Padova, Padova, Italy*
[28] *Ospedale Treviso, Treviso, Italy*
[29] *Ospedale Venezia Mestre, Venezia, Italy*
[30] *Ospedale Vicenza, Vicenza, Italy*

Background/aim: Direct-acting antivirals (DAAs) have revolutionized treatment of hepatitis C virus (HCV). We investigated DAA effectiveness and evolution of treatment schedules in a large real-life Italian setting.

Methods: Consecutive HCV patients starting DAAs between December 2014 and June 2017 in 58 hepatology centers with available sustained virological response (SVR12) data were enrolled.

Results: 8637 patients were included: age was 59 (18–90) years, 62% males, ALT 75 (10–1261), platelet count 138 (11–772) $\times 10^3$/ml, LSM 14.8 (3.0–75.0) kPa. 63% of patients had cirrhosis (CPT A in 75%), 21% had bridging fibrosis (AIFA criteria 1 and 4). HCV genotype was 1 in 57%, (1b in 41%, 1a in 16%), 2 in 13%, 3 in 13%, 4 in 9%. 33% of patients had previous treatment experience. Most prescribed DAA combinations were Sofosbuvir (SOF)/Ledipasvir in 31% of patients, Paritaprevir/Ombitasvir/ritonavir + Dasabuvir in 19%, SOF in 17%, SOF + Daclatasvir in 15%, SOF + Simeprevir in 13%. 1% of patients received Grazoprevir/Elbasvir or SOF/Velpatasvir. Ribavirin was added in 67% of schedules. Treatment duration was 12 weeks in 59% of cases, 24 weeks in 36%. An SVR was achieved by 95% of patients, treatment failures were mostly cirrhotics (62%) and HCV genotype 1 or 3 (67%). 5247 and 3390 patients started treatment in 2014–2015 and 2016–2017, respectively, due to DAA prescribing limitations being eliminated in early 2017. By comparing treatment schedules across different time periods, the 24-week duration declined from 41% of treatments in 2014–2015 to 28% in 2016–2017, while Ribavirin was used in 81% of regimens compared to 58%, respectively ($p < 0.0001$ for both comparisons). SVR rates improved in the second treatment period (94% in 2014–2015 vs 97% in 2016–2017, $p < 0.0001$).

Conclusions: DAA treatments progressively evolved overtime in a real-life multicentre setting with increased effectiveness; regimen simplification is expected to allow treatment scale-up in near future.

https://doi.org/10.1016/j.dld.2018.01.058

F-21

HCV clearance and pro-thrombotic shift in advanced liver disease

E. Biliotti[1], D. Palazzo[1], R. Cangemi[2], R. Carnevale[3], R. Esvan[1], L. Fontanelli-Sulekova[1], C. Franchi[1], P. Maida[1], C. Nocella[3], P. Perinelli[1], M. Santori[1], M. Spaziante[1], F. Tamburini[1], F. Violi[2], G. Taliani[1]

[1] *Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy*
[2] *Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy*
[3] *Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy*

Introduction: Hepatitis C virus (HCV) infection is associated to an increased risk of cardiovascular-disease (CVD) and thromboembolic-events. Direct-acting-antiviral (DAA) agents have an excellent safety profile and induce HCV viral clearance in almost all treated patients, but their impact on CVD risk remains unclear. Platelet activation and oxidative stress play a crucial role on the onset of thrombosis and CVD.

Aim: We investigated the levels of urinary thromboxane B2 (TxB2), a marker of platelet activation, and 8-iso-prostaglandin F2α (8-iso-PGF2α), a marker of oxidative stress, during and after DAA treatment in HCV-patients with advanced liver disease.

Materials and methods: We enrolled 90 consecutive HCV-patients with advanced fibrosis (Metavir F3–F4) who achieved SVR after DAA-treatment (65.6% with ribavirin, 77.8% with sofosbuvir). Urinary levels of TxB2 and 8-iso-PGF2α were measured at baseline (T0), end-of-treatment (EOT) and after 12-weeks of follow-up (FU) by ELISA commercial kits. Statistical analysis was performed by IBM-SPSS-version-21.0.

Results: The characteristics of enrolled patients were: age 59.3 ± 10.8 years, 58.9% males, BMI 25.0 ± 3.6, 75.6% HCV-Gt-1, HCV-viral-load 6.1 ± 0.8 Log 10 IU/mL, platelet 156.0 × 10^6/mm^3, liver stiffness 19.7 ± 12.7 kPa). Urinary TxB2 levels increased sharply and significantly during antiviral treatment (161.5 [150.0–188.5] vs 230.0 [185.0–265.0] ng/mg creatinine, $p < 0.001$) with a small further increase during FU (242.5 [179.7–298.5] ng/mg creatinine, $p = 0.057$). Conversely, urinary 8-iso-PGF2α levels increased steadily during therapy (150.0 [136.5–161.0] vs 165.0 [151.5–210.0] pg/mg creatinine, $p < 0.001$) and FU (210.0 [167.5–255.0] pg/mg creatinine, $p < 0.001$). A significant correlation between TxB2 and 8-iso-PGF2α levels increase was observed during the study period ($r = 0.421$, $p < 0.001$). Platelet levels modifications did not correlate neither with TxB2 ($r = -0.043$, $p = 0.48$) nor with 8-iso-PGF2α increase ($r = -0.027$, $p = 0.66$) and no clinical, biochemical, virological or treatment factors were found to correlate with TxB2 and 8-iso-PGF2α level changes.

Conclusions: The fast and significant increase of TxB2 and 8-iso-PGF2α levels observed in patients with advanced fibrosis successfully treated with DAA might indicate a shift toward a pro-thrombotic profile concomitant with viral clearance. These findings support the potential need of an antithrombotic prophylaxis administration early on treatment with DAA therapy.

https://doi.org/10.1016/j.dld.2018.01.059

F-22

Galectin-3+ cells in the liver associate with tissue damage in children with NAFLD

N. Panera [1], F. Oliveira [2], C. De Stefanis [1], A. Crudele [1], V. Nobili [1], A. Alisi [1]

[1] *Research Area for Multifactorial Diseases, Children's Hospital Bambino Gesù, Rome, Italy*
[2] *Institute of Biomedical Sciences, Federal University of Rio de Janeiro, Brazil*

Introduction and aim: Non-alcoholic fatty liver disease (NAFLD) is a complex disease described by a wide spectrum of liver disorders ranging from early steatosis to non-alcoholic steatohepatitis (NASH), the latter characterized by lobular inflammation, balloon degeneration and fibrosis. The role of *macrophage* polarization (*M1/M2*) and inflammatory signals appears to be central for pathogenesis and progression of NAFLD. Galectin-3 (Gal-3), a multifunctional β-galactoside binding protein firstly described on the surface of macrophages, has been associated with fibrosis in distinct tissues, including the liver, but the role of this protein in NAFLD remains controversial. Here, we investigated whether Gal-3 expression in liver cells may associate with tissue damage in children with NAFLD.

Materials and methods: In this work, liver biopsies from 40 children with NAFLD were stained with antibodies against classical markers of macrophages (CD68 and CD206) and Gal-3. The images were acquired by confocal microscopy and quantitative image analysis of each staining was performed and compared to histologic traits.

Results: We found that the number CD68+/CD206+ cells (markers of M2) was significantly reduced in patients with NASH, and inversely correlated with steatosis and ballooning. The same trend was observed in the number of both Gal-3+ and Gal-3+/CD68+ cells. Moreover, we observed that all macrophages Gal-3+/CD68+ also co-expressed CD206, thus the number of Gal-3+/CD68+/CD206+ macrophages was significantly decreased in the liver of patients with NASH. No correlation of these co-expressed markers with inflammation and fibrosis was observed. Furthermore, Gal-3+/α-SMA+ cells were significantly increased in patients with NASH and the percentage of these double-positive cells correlated with fibrosis.

Conclusions: Our data demonstrated that the number of Gal-3+ cells associated with tissue damage in different ways suggesting a dual role of this protein in the pathogenesis of pediatric NAFLD, even if this and clinical application of Gal-3 inhibitors for therapy deserve further studies.

https://doi.org/10.1016/j.dld.2018.01.060

F-23

Monofocal hepatocellular carcinoma (HCC): Is diameter so important? Analysis on the Italian Liver Cancer (ITA.LI.CA) database between BCLC algorithm and Milan criteria

G. Peserico [1], B. Penzo [1], F. Pelizzaro [1], A. Imondi [1], A. Meneghetti [1], A. Sartori [1], M. D'Elia [1], A. Vitale [1], F. Trevisani [2], F. Farinati [1]

[1] *Department of Surgery, Oncology and Gastroenterology, University of Padova, Padua, Italy*
[2] *Department of Medical and Surgical Science, University of Bologna, Bologna, Italy*

Background and aims: This study aimed at evaluating the role of the 5 cm diameter's cut-off of the Milan Criteria in correctly staging and treating "early" monofocal HCC.

Patients and methods: 1623 monofocal HCC, diagnosed between 2001 and 2014 by the ITA.LI.CA group and stratified by diameter in 1345 HCC >2/≤5 cm (SMALL) and 278 HCC >5 cm (LARGE), were analysed. Among them 1087 were "early" monofocal HCC. They were compared to 1048 BCLC B stage HCC and sub-grouped according to the adherence to the guidelines for resection. Statistics included Chi-square, Kaplan–Meier (Log-rank) and Cox multivariate analysis.

Results: Overall median survival was 38 months (C.I.: 36–41), with 41 months (C.I.: 38–45) in SMALL HCC and 21 (C.I.: 17–26) ($p < 0.0001$) in LARGE HCC. At multivariate analysis, the two subgroups presented different predictors of survival and statistically different therapeutic choices. Surgery provided the best survival. BCLC B HCC median survival was similar to that of LARGE HCC. According to adherence, the largest subgroup (57%) included the patients resected out of the BCLC criteria, especially in LARGE HCC (64%); at multivariate analysis the nodule diameter was the only independent predictor of survival ($p < 0.0001$). Similar results were obtained analysing the subgroup of 1087 "early stage" monofocal HCC, with a 49 months survival in the 924 SMALL HCC and 31 months in the 163 LARGE HCC ($p < 0.01$).

Conclusions: The 5 cm cut-off – supported by Milan criteria – stratifies monofocal (early or not) HCC in two categories that show different survival, predictors and therapeutic choices. Single HCC >5 cm have a median survival comparable to HCC in the BCLC B stage. In monofocal HCC best results are obtained by surgery, with the best survival in SMALL HCC. Resection is recommended also in large tumors.

https://doi.org/10.1016/j.dld.2018.01.061

F-24

Liver transplant organ allocation; preliminary results using the ISO score system

A. Bertacco, E. Dalla Bona, A. Vitale, M. Di Giunta, M. Polacco, R. Boetto, D. Bassi, U. Cillo

Department of Surgery, Oncology and Gastroenterology, Hepatobiliary Surgery and Liver Transplantation, Padua University, Padua, Italy

Background: Liver transplant (LT) is the best curative treatment for patient with end-stage liver disease, but is limited by organ supply. Organ allocation is a crucial issue; recently a new score, the ISO score has been adopted in Italy to garantee balance in organ allocation based on urgency, utility and transplant benefit principles.

Material and methods: Two groups of patients awaiting LT in our center were considered: a study group (273 patients) defined by patients in waiting list in the period January 2016–December 2016 and allocated using the ISO score system and a control group (398 patients) allocated with the previous allocation system in the period January 2014–December 2015. LT probability and rate of dropout was calculated using a competing risk analysis. An intention to treat analysis was performed to define overall survival for all patients listing for LT. Univariate and multivariate analysis was conducted.

Results: No difference in intention to treat analysis or rate of drop out was observed between the 2 groups. Age and HCC resulted predictors of poor outcome in control group and study group respectively. Using a competing risk analysis the probability of LT resulted similar among groups; variables influencing LT in the study were age, presence of HCC and MELD while only MELD resulted significant in the control group. Dropout was higher for HCC stratum 3 in study group and HCC stratum 1 and 2 in control group.

Conclusion: Preliminary results in using ISO score allocation system demonstrated comparable rate of LT and patients dropout. ISO score appears to be a transparent and easily applicable allocation system able to guarantee a uniformity of list management and organ allocation in an extremely heterogeneous scenario as the Italian organ transplant.

https://doi.org/10.1016/j.dld.2018.01.062

F-25

Predictors of hepatocellular recurrence after liver transplant in Hepatitis C patients: A ten-years single center cohort

M. Iavarone [1], M.F. Donato [1], F. Invernizzi [1], M.A. Manini [1], S. Monico [1], A. Sangiovanni [1], M. Maggioni [2], P. Reggiani [3], G. Rossi [3], P. Lampertico [1]

[1] *A.M. & A. Migliavacca Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Maggiore Hospital, University of Milan, Italy*
[2] *Department of Pathology, Fondazione IRCCS Ca' Granda Maggiore Hospital, Milan, Italy*
[3] *HBP Surgery and Liver Transplantation Unit, Fondazione IRCCS Ca' Granda Maggiore Hospital, University of Milan, Italy*

Background and aim: Liver transplantation (LT) is a well-established treatment for HCV-related cirrhosis and HCC within "Milan criteria" (MC) with a reported recurrence rate of 16%. Recently contradictory results on HCC recurrence in HCV patients treated with DAA emerged. The study aims to identify biological and clinical predictors of HCC recurrence and to report overall survival (OS) post-LT in HCV-cirrhotic patients with HCC.

Patients and methods: Between November 2004 and August 2016, 108 HCV consecutive cirrhotic patients underwent LT for HCC (81% males, age 57 years, 56% genotype 1, 22% HCV-RNA negative at LT, 33% non-responder to previous IFN-therapy, 30% treated by DAA). At LT median AFP was 10 ng/ml (1–5655). At explant pathology: 78% were within MC, median viable neoplastic nodules were 2 (0–9), 22% showed microvascular invasion, 47% with Edmonson score ≥3 and 3 cases showed mixed HCC/cholangiocarcinoma (iCC).

Results: During 46 months of post-LT follow-up (1.5–158), HCC recurred in 14 patients (extra-hepatic 86%) after 16 (4–90) months, with a 3-year cumulative probability of 9%. Among them: 5 were beyond MC, 7 with vascular invasion, 11 had Edmonson score ≥3 or mixed HCC/iCC; 9 patients were HCV–RNA negative at the time of recurrence (4 after IFN, 5 after DAA pre-LT). At univariate analysis vascular invasion (HR 4.3, 95%CI 2.0–9.2, $p < 0.001$) and Edmonson score 3 or mixed HCC/iCC (HR 7.4, 95%CI 1.6–33.7, $p = 0.009$) predicted HCC recurrence. These predictors were confirmed by multivariate analysis (HR 2.7, 95%CI 1.1–6.1, $p = 0.019$ and HR 9.2, 95%CI 1.1–76, $p = 0.04$, respectively). Twenty-four patients died after of 31 months (1.5–94): 5 for HCC progression, 5 due to HCV recurrence, 7 for sepsis, 5 for non-liver tumors and 2 for surgical complications. Five-years OS was 77%.

Conclusions: In our series of HCV-HCC transplanted patients, only tumor-related histological features at explant pathology predicted HCC recurrence.

https://doi.org/10.1016/j.dld.2018.01.063

F-26

Video-laparoscopic MW ablation in a European high volume center: Safety and efficacy of 891 procedures

A. Bertacco [1], A. Vitale [1], A. Marchini [1], E. Fasolo [1], F. D'Amico [1], E. Gringeri [1], D. Neri [1], D. Bassi [1], R. Carandina [2], C. Aliberti [2], U. Cillo [1]

[1] *Department of Surgery, Oncology and Gastroenterology, Hepatobiliary Surgery and Liver Transplantation, Padua University, Padua, Italy*
[2] *Oncology Radiodiagnostics Department, Oncology Institute of Veneto, Institute for the Research and Treatment of Cancer (IRCCS), Padua University, Padua, Italy*

Background: Video-laparoscopic (VLS) MW ablation (MWA) is not considered in the international guidelines as a standard therapy for HCC patients. Our center evaluated safety and efficacy of VLS MWA as a therapeutic option for the treatment of HCC patients not suitable for resection or percutaneous ablation.

Methods: A retrospective analysis of a prospective database on HCC patients treated with VLS MWA from August 2009 to September 2016 at our institution was performed. Patient demographics, operative characteristics and complications were collected. Statistic analysis was performed to identify overall survival and recurrence rate.

Results: 891 VLS MWA were performed in 679 patients; mean age was 65 years. Mean MELD was 10; 31.9% of patients were Child B, 42.2% were BCLC B-C. No perioperative mortality was observed. Six-months mortality was 7.9%. The overall morbidity was 30.1% with Clavien complications ≥3 in 1.9%; median LOS was 2 days. In 351 cases (39.4%) VLS MWA was the first line therapy. Overall 1-

, 3-, 5-yr survival was respectively 81%, 50% and 32%. Radiologic imagines revision was possible for 630 nodules; complete ablation was achieved in 83% of the treated nodules.

Conclusions: In a high volume center VLS ablation resulted safe and effective in the mininvasive treatment of HCC patients. Improvements in middle term results may be achieved through an increased accuracy in the patient selection process with particular reference to performance status, liver function and tumor stage evaluation.

https://doi.org/10.1016/j.dld.2018.01.064

F-27

Validation of the EASL 2017 HBV Clinical Practice Guidelines criteria for switching patients long-term treated with Tenofovir Difumarate to Entecavir or Tenofovir Alafenamide in a real-life setting

A. Loglio[1], G. Grossi[1], R. Soffredini[1], M. Borghi[1], F. Facchetti[1], E. Galmozzi[1], R. Perbellini[1], G. Lunghi[2], P. Lampertico[1]

[1] *CRC "A. M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy*
[2] *Virology Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy*

Background and aims: The 2017 EASL HBV CPG recommend switching TDF treated patients to TAF (NUC naïve or experienced) or ETV (only NUC naïve) if they have one of the following risk factors: (1) age >60 years, (2) bone disease [history of fragility fracture, osteoporosis, chronic use of steroids or medications that worsen BMD], and (3) renal alterations [eGFR <60 mL/min, albuminuria >30 mg/24 h or moderate dipstick proteinuria, low serum phosphate (<2.5 mg/dL), or hemodialysis]. We want to estimate the number of patients who could benefit from this switch in a cohort of TDF-treated patients.

Methods: All consecutive CHB subjects on TDF before 31 Dec 2016 were enrolled in a cross-sectional real-life study at the control blood sample, between Jan and 31 Jun 2017.

Results: 414 patients were enrolled: 63 (22–88) yr, 79% HBeAg negative, 76% males, 44% cirrhotics, treated by TDF for 93 (9–133) months, 34% on a reduced dose, 95% undetectable HBV DNA, 53% NUCs previously treated, 39% arterial hypertension, 10% diabetes, BMI 25 (16–42) kg/m^2. Bone safety: 54% osteopenia and 12% osteoporosis at spine (available DEXA in 86%. Renal alterations: 23% GFR (by CG formula) <60 mL/min (70% already on a reduced TDF dose), 21% low serum phosphate, 17% increased albuminuria, 5% moderate dipstick proteinuria, 58% increased UBCR (>300 μg/g), 66% hyperphosphaturia (<0.80 TmPO4/GFR ratio). By applying EASL criteria, 57% were >60 years (1), 13% had osteoporosis or were steroid-treated (2), and 41% had reduced GFR, hypophosphatemia or albuminuria/proteinuria (3). Overall, 69% had at least one criterion, 6% all criteria (1 + 2 + 3), 8% age and bone criteria (1 + 2) and 8% bone and renal criteria (2 + 3). 33% met both the age and renal criteria (1 + 3).

Conclusions: 2/3 of CHB long-term TDF-treated patients in a real-life setting are candidates to a ETV or TAF switch according to EASL 2017 criteria.

https://doi.org/10.1016/j.dld.2018.01.065

F-28

National quality control and validation of hepatitis C NS3, NS5A and NS5B genotypic resistance testing

T. Ruggiero[1], V. Cento[2], M. Aragri[2], M. Arosio[3], F. Baldanti[4], M. Brunetto[5], B. Bruzzone[6], E. Boeri[7], D. Cavallone[5], N. Coppola[8], M. Di Stefano[9], V. Ghisetti[1], A.P. Callegaro[3], M.R. Capobianchi[10], C. Caudai[11], N. Cuomo[12], S. Galli[13], E. Galmozzi[14], A.R. Garbuglia[10], W. Gennari[15], A. Lai[16], S. Menzo[17], V. Micheli[18], C. Minosse[10], L. Monno[19], S. Paolucci[4], T. Pollicino[20], A. Raddi[12], G. Raffa[20], G. Raimondo[20], M. Sanguinetti[21], M. Sampaolo[7], R. Santangelo[21], T. Santantonio[9], S. Soldini[21], M. Starace[8], M.L. Vatteroni[22], A. Craxì[23], C.F. Perno[24], F. Ceccherini-Silberstein[2], M. Zazzi[11], on behalf of HCV Virology Italian Resistance Network (VIRONET C)

[1] *Microbiology and Virology Laboratory – Amedeo di Savoia Hospital ASL Città di Torino, Torino, Italy*
[2] *Department of Experimental Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy*
[3] *Microbiology and Virology, ASST Papa Giovanni XXIII, Bergamo, Italy*
[4] *MolecularVirology, IRCCS Policlinic Foundation San Matteo, Pavia, Italy*
[5] *Hepatology Unit, Azienda Ospedaliero-Universitaria Pisana, Italy*
[6] *Hygiene Unit – Ospedale Policlinico San Martino Genova, Italy*
[7] *Microbiology e Virology Unit, Ospedale San Raffaele, Milano, Italy*
[8] *Infectious Disease Department, University of Campania "Luigi Vanvitelli", Napoli, Italy*
[9] *Infectious Diseases Unit, Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy*
[10] *Virology Laboratory, INMI Lazzaro Spallanzani, Roma, Italy*
[11] *Department of Medical Biotechnology, Universityof Siena, Policlinico S. Maria alle Scotte, Siena, Italy*
[12] *Microbiology and Virology Laboratory, Azienda Ospedaliera dei Colli, Cotugno-Napoli, Italy*
[13] *Microbiology Unit, Ospedale S.Orsola-Malpighi, Bologna, Italy*
[14] *Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Milano, Italy*
[15] *Microbiology and Virology Unit, University Hospital Policlinico of Modena, Modena, Italy*
[16] *ASST Fatebenefratelli Sacco Hospital, Milano, Italy*
[17] *Virology Laboratory, Ospedali riuniti di Ancona, Ancona, Italy*
[18] *Clinical Microbiology, Virology and Bioemergencies, ASST Fatebenefratelli Sacco, Milano, Italy*
[19] *Infectious Disease Department, Azienda Ospedaliera Policlinico di Bari, Bari, Italy*
[20] *Department of Internal Medicine, Azienda Ospedaliera Universitaria Policlinico "G Martino", Messina, Italy*
[21] *Institute of Microbiology, Policlinico Universitario Agostino Gemelli, Roma, Italy*

[22] *Virology Laboratory, Azienda Ospedaliero-Universitaria Pisana, Italy*
[23] *Gastroenterology, "P. Giaccone" University Hospital, Palermo, Italy*
[24] *University of Milan, Milan, Italy*

Introduction and aim: International guidelines recommend HCV genotypic-resistance-testing (GRT) in selected cases, however, GRT application is limited in many countries by the lack of a commercial-assay. Within the Italian VIRONET-C, we conducted a multicentre HCV Sanger-GRT quality control study with the aim of providing a standardized GRT at National-level.

Material and methods: A panel of 10 blinded samples with HCV-genotypes (GT)1a-1b-2c-3a-4a-4d was provided to 23 laboratories of VIRONET-C.NS3-NS5A-NS5B GRT was performed by using different Sanger sequencing-protocols at 22 laboratories, while Illumina next-generation-sequencing (NGS) was performed at 1 laboratory, and used as comparator with 15% detection cut-off.

Results: Fourteen laboratories generated all the 30 expected sequences, while the remaining 8 generated a mean ± SD of 24.3 ± 3.6 sequences. Fourteen laboratories used the same Sanger-protocol while the others used a unique system. Geno2pheno tool identified 7 resistance-associated-substitutions (RASs) in the 30 sequences generated by NGS. Comparing the NGS-sequences to all available Sanger-sequences four major RASs discordances were observed: a NS5A-Y93H and a NS3-Q168QK detected by 100% and 35% Sanger-reactions, respectively, but not by NGS, and a NS5B-S556G detected by NGS (98% prevalence) in 2 samples (GT-3a and GT-2c) but not by any Sanger-reaction. When excluding these discrepancies, the overall Sanger accuracy with respect to the consensus sequence was 85%. The rate of sequencing success was almost equal among the laboratories using the same assay *vs* the others (86% *vs* 85% respectively). The overall RAS detection disagreement among laboratories was 9% in NS3, 7% in NS5A, 0% in NS5B.

Conclusions: Most of the laboratories of the Italian VIRONET-C provided HCV-GRT results for all circulating HCV-GTs and all clinically relevant genes. Accuracy and inter-laboratory precision were affected by the use of different methods, highlighting the challenge of HCV variability. Quality control programs for HCV-GRT should be promoted to allow its fruitful use in optimizing HCV treatment.

https://doi.org/10.1016/j.dld.2018.01.066

F-29

Right timing for transient elastography lead the right follow up after HCV treatment

L. Scribano, D. Caroli, E. Rosa Rizzotto, L. Peraro, D. Martines, F. De Lazzari, S. Lobello

S.C. Gastroenterologia, Ospedale Sant'Antonio AULSS 6 Euganea, Padova, Italy

Background: The improvement of liver fibrosis assessed using transient elastography (TE) by FibroScan® is leading to new insights in the concepts of fibrosis regression. The possibility of using new direct antiviral agents (DAA) in cirrhotic patients, previous excluded from PegInterferon treatment for risk of hepatic failure, has permitted to verify the hypothesis of fibrosis regression in these patients. TE should be interpreted taking into account the inflammatory profile associated with hepatitis.

Aim: To establish the stiffness variations in a court of HCV-patients before and after antiviral treatment to assess the correct follow up in patients with high stiffness value.

Patients and methods: We enrolled 246 consecutive patients treated with DAA for chronic hepatitis C. TE and blood tests were performed before therapy and during follow-up.

Results: Each patient underwent TE before therapy; 60 of them performed TE at 24th weeks after end of treatment (EOT) and also at 24th months after EOT. Before therapy, 91 of 246 patients (37%) had stiffness >12 kPa (suggestive of advanced fibrosis stage); all 91 had a Child–Pugh score A5 but only 49 (56%) had APRI score suggestive of cirrhosis. Regardless of DAA-schedule, all 246 patients reached SVR. At follow-up only 3 patients presented stiffness >12 kPa (5%) and they were the same patients who maintained APRI score >1. Respect to the basal stiffness, after therapy all patients showed a significant decrease at 24th week after EOT (mean 14.9 kPa *vs* 9.5 kPa, $P = 0.0009$). This decay was unchanged at 24th months after EOT (mean 9.5 kPa *vs* 8 kPa, P = NS).

Conclusions: The sudden improvement of liver stiffness assessed by TE within the 24th week after EOT could be related to the "switch-off" of necro-inflammatory activity achieved by antiviral therapy. Follow-up should be established regarding APRI score and TE performed at 24th week after EOT instead of the pre-treatment values.

https://doi.org/10.1016/j.dld.2018.01.067

F-30

Oleuropein and copper: New perspectives against liver disease

C. Balsano, C. Porcu, S. Sideri, S. Tavolaro

Department of Life, Health & Environmental Sciences MESVA, University of L'Aquila, L'Aquila, Italy

Introduction: Diet significantly affects health. Incorrect feeding results in overweight or obesity that are associated with liver steatosis, a pathological condition that affects about 30% of the world's population. This pathology, characterized by accumulation of fat in the liver, inflammation and ballooning, can progress toward cirrhosis and hepatocarcinoma (HCC). In such processes, transition metals (copper, zinc, Fe, etc.) play a key role. Accordingly, altered copper homeostasis has been observed in various stages of NAFLD. Mediterranean diet has beneficial effects on health, and olive oil is one of the main actors. Oleuropein (Ole), a phenolic compound derived from green olives and olive leaves, is able to bind copper.

Aim: Hence, we evaluated the correlation between Ole and intracellular copper concentration and its role in counteracting liver damage related to high fat diet intake (HFD).

Materials and methods: Real-time PCR, atomic absorption, Bio-Plex multiplex biometric ELISA-based immunoassays, adipored and western blots were performed for *in vitro* and *in vivo* experiments.

Results: *In vitro*, fatty acids induce intracellular copper modulation. Oleuropein leads to a significant reduction in both the intracellular content of Cu and lipid accumulation. In a HFD mouse model treated with Ole we highlighted a significant reduction in levels of Cu in liver tissue, hepatic steatosis and related inflammatory conditions. In particular, the levels of chemokines MCP1 and CXCL1, both correlated with the progression of liver disease, were significantly reduced. The involvement of genes (e.g. *tp53*, *Myc*, etc.), involved in the control of the entry and efflux of copper in cells, is under investigation.

Conclusions: Our results demonstrate that Ole has inhibitory effects on the progression of liver disease that correlate with its ability to modulate copper.

https://doi.org/10.1016/j.dld.2018.01.068

F-31

Liver function tests do not predict liver damage in diabetes. Analysis of liver steatosis and fibrosis by transient elastography in routine diabetes care

R. Lombardi, L. Airaghi, V. Borroni, C. Bertelli, L. Burdick, E. Fatta, F. Iuculano, S. Pelusi, L. Valenti, S. Fargion, A.L. Fracanzani

Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital University of Milan, Milan, Italy

Introduction: Diabetes is a risk factor for the onset of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis. Liver biopsy is the gold standard for staging liver disease but it is not routinely applicable to the wide and otherwise asymptomatic diabetic population.

Aim: To non-invasively estimate prevalence and predictors of NAFLD and fibrosis in a cohort of diabetic patients.

Materials and methods: Ninety-seven consecutive patients attending the outpatient diabetes clinic without any liver disease underwent liver ultrasound and transient elastography (FibroScan®). Controlled attenuation parameter (CAP) >250 Db/m and liver stiffness measurement (LSM) >7.9 kPa defined the presence of steatosis and fibrosis.

Results: Mean age 65 ± 6 years, 71% of patients males, all patients on anti diabetic therapy (oral agents in 84% and insulin in 16%). Hypertension in 80% of patients, dyslipidemia in 83% (74% on statins), overweight in 75% and obesity in 27%. Deranged AST, ALT and GGT in 1%, 6% and 7% of patients. Prevalence of hepatic steatosis was 78% at FibroScan® by CAP and 91% at US. CAP values significantly correlated with US steatosis grades (p for trend = 0.006). CAP >250 Db/m was associated at multivariate analysis only with plasmatic insulin (OR 1.14, 95% C.I. 1.0–1.3). LSM >7.9 was present in 8% of patients and was associated with BMI ($p = 0.001$), ALT ($p = 0.001$), GGT ($p = 0.0001$), insulin levels ($p = 0.001$) and CAP values ($p = 0.001$) at age and gender adjusted analysis. No association between any anti-diabetic drugs or complications and either steatosis or fibrosis was observed.

Conclusions: NAFLD is highly prevalent in diabetic patients, liver fibrosis is present in nearly 10% of them and liver function tests are unable to detect liver damage. We suggest the use of revised normal values of liver function tests for diabetic patients and most importantly a careful screening for liver disease in diabetics in primary care.

https://doi.org/10.1016/j.dld.2018.01.069

F-32

Primary Biliary Cholangitis (PBC): The emotional perception of the disease journey from a patient's perspective

D. Alvaro[1], B. Marini[2], C. Bassanelli[2], E. Coretti[3], N. Cazzagon[4], M. Margotti[5], P. Andreone[5], L. Muratori[5], V. Calvaruso[6], P. Invernizzi[7], M. Marzioni[8], A. Benedetti[8], A. Craxì[6], A. Floreani[4]

[1] *Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy*
[2] *Intercept Italia srl, Milan, Italy*
[3] *GFK Italia srl, Milan, Italy*
[4] *Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy*
[5] *Department of Medical and Surgical Science, University of Bologna, Bologna, Italy*
[6] *Gastroenterology and Epatology, DIBIMIS, Università di Palermo, Palermo, Italy*
[7] *Department of Medicine and Surgery, University of Milan Bicocca, Milan, Italy*
[8] *Clinics of Gastroenterology, Univerità Politecnica delle Marche, Ancona, Italy*

Introduction: PBC is a rare cholestatic liver disease that may progress to liver decompensation and death. Due to the rarity, heterogeneous form of presentation and natural history, diagnosis may be delayed and the burden of disease underperceived.

Aim: The aim of this project was to gather patient insight by exploring key domains of the PBC journey to diagnosis, the impact of the disease on patient lives and the potential unmet needs.

Method: Patients affected by inadequately controlled PBC, underwent face to face interviews with a psychologist and filled over one e-diary, in which they may use free text and chose images and video to express their feelings. Key words written by patients were analyzed using T-lab software, which provide a statistical and linguistic analysis of a text mining.

Results: Twenty-one patients were enrolled. The journey to diagnosis for PBC patients is complex: most patient felt that their diagnosis unnecessarily delayed and the communication with point of care suboptimal. At diagnosis the most reported feelings were lack of empowerment and solitude. Higher socio-economic status or milder symptoms correlated with better proactivity and capacity to manage the disease. Lower schooling was associated with depression, passive or fatalistic approach to disease, regardless of severity of symptoms.

Conclusions: PBC severely affects quality of life of patients, both from a physical and psychological perspective. Treatment success and a holistic approach to disease management are the key drivers for a positive vision of the future. The impact of PBC is more severe on patients with lower cultural background and poor affective and social support. The management of a patient's journey could be improved by supporting early diagnosis and easier referral to expert centers, improving communication, and offering psychological support to patients, their families and caregivers.

https://doi.org/10.1016/j.dld.2018.01.070

F-33

Technical assessment and reliability of controlled attenuation parameter (CAP) with M probe in NAFLD

A. Salmi [1], P. Campagnola [2], C. Ferrari [3], L. Frulloni [2]

[1] *Liver Unit, San Camillo, Brescia, Italy*
[2] *UO Gastroenterologia B, Azienda Ospedale Università, Verona, Italy*
[3] *Statistic Unit, IRCCS San Giovanni di Dio Fatebenefratelli, Brescia, Italy*

Introduction and aims: In clinical practice the use of imaging and liver biopsy is changing [1]. Risk stratification and prognosis of liver disease is accepted for HCV, HBV etiology and proposed for NAFLD (non alcoholic fatty liver disease) patients (pts) through non invasive fibrosis and fatty liver assessment like liver stiffness measurement (LSM) by transient elastography (TE) who can be performed together with controlled attenuation parameter (CAP); we aimed to compare CAP results in our real life experience with recently proposed cut off related to optimal stratification of steatosis [2] and reliability [3].

Methods: 950 patients were consecutively examined in twelve months, 36 excluded for technical failure in one case for obesity, 35 (3.6%) for TE-IQR/TE-Med >30%. Of 914 valuable pts disease etiology: HCV 524 (57.3%), NAFLD 221 (24.2%), HBV 60 (6.6%), and Others 109 (11.9%) were examined by FibroScan® CAP (Echosense Paris). CAP value groups were defined according to recently proposed cut off (2): S0 (<248), S1 (248), S2 (268), S3 (280) and CAP IQR (by ANOVA test for continuous variable and Chi squared test for categories variable.

Results: In 914 pts steatosis distribution was 46,9%, 13.2%, 7%, 32.8% for S0, S1, S2, S3; CAP-median dB/m cutoff >280 (S3) was associated with male gender, high TE-median kPa value, in 24.8% of HCV and 57.4% of NAFLD etiology; mean TE kPa median value distribution was 8.5; 7.5; 8.6; 9.5 for S0, S1, S2, S3; CAP-IQR >40 occurred in 31%. In NAFLD pts 45 of 132 (20%) CAP-IQR >40 occurred; TE-kPa median value (>10.5; 7.0–10.5; <7) defined high, intermediate, low risk of progression in (11%), 7.0–10.5 (7%).

Conclusions: In NAFLD group applying CAP-IQR >40 20% of pts could have low validity steatosis grade stratification. S3 grade defined by 280 dB\m cut off occurred in one of four pts with HCV etiology and 57% with NAFLD etiology.

References

[1] Elliot B. N Engl J Med 2017;377:756–68.
[2] Karlas T. http://dx.doi.org/10.1016/j.jhep.2016.12.022.
[3] Wong VW. http://dx.doi.org/10.1016/j.jhep.2017.05.005.

https://doi.org/10.1016/j.dld.2018.01.071

F-34

HCV-FiS (HEpatitis C Virus Finger-stick Study): HCV RNA point-of-care testing by GeneXpert in the setting of DAA therapy

F. Bronte [1], V. Calvaruso [1], D. Ferraro [2], S. Petta [1], B. Magro [1], V. Di Marco [1], A. Craxì [1]

[1] *Sezione di Gastroenterologia & Epatologia, Di.Bi.M.I.S., University of Palermo, Italy*
[2] *Sezione di Virologia Dip. PRO.SA.M.I., University of Palermo, Palermo, Italy*

Background and aims: Highly effective and tolerable DAA regimens have simplified HCV patient care but HCV-RNA assessment during and after therapy still requires blood collection and transport to a specialized laboratory, compromising linkage to care. GeneXpert HCV-Viral-Load (GXHVL, Cepheid, Sunnyvale, CA, USA) is a plasma-based assay with a sensitivity $\leq$10 IU/mL which provides results within 2 h. We evaluated the performance of GXHVL with a modified protocol for point-of-care (POC) testing using finger-stick capillary whole-blood samples in the setting of HCV outpatient [1].

Methods: 59 consecutive HCV-patients were enrolled. Capillary blood collected by finger-stick was processed on site on the GeneXpert platform. HCV-VL was tested on a simultaneous venous blood sample by the Hospital's Virology Lab using a Real Time(RT)-PCR (Roche TaqMan). Patients had DAAs according to the current recommendations. GXHVL and Taqman assay were compared at baseline(BL), at week 4(W4), at end-of-therapy(EOT) and at week 12 of follow-up.

Results: 57 patients (mean age; 65.8 $\pm$ 12.1 years; males: 54%) were tested with both assays, 2 were excluded due to mishandling of the GXHVL specimen at BL. At BL 56/57 (98.2%) were HCV-RNA positive. In one patient HCV-RNA was undetectable by both methods (positive by TaqMan two months earlier). Linear regression analysis confirmed the high concordance in HCV-RNA quantification between GXHVL and the RT-PCR assay (R2: 0.654; $p < 0.001$) at BL (median VL: 778,400 vs 1,230,000 IU/ml respectively). At W4, 39/56 (69.6%) and 42/56 (75%) patients had undetectable HCV-RNA by GXHVL and RT-PCR test, respectively. Both assays demonstrated undetectable HCV-RNA in all 56 patients (100%) at EOT. At SVR12 both assays identified the single case of HCV relapse in the cohort (HCV-RNA: 248,600 vs 822,000 IU/ml by GXHVL and RT-PCR respectively) with a concordance rate, sensitivity and specificity of 100%.

Conclusion: GeneXpert as a POC assay used in the outpatient setting, provides results fully comparable to the laboratory-based test. Its excellent performance and ease of use suggest its adoption in non-specialist settings where simplicity of care is paramount to implement HCV eradication campaigns.

Reference

[1] Grebely J. Lancet Gastroenterol Hepatol 2017.

https://doi.org/10.1016/j.dld.2018.01.072

F-35

Role of nutritional intake on clinical presentation of lean and overweight NAFLD

G. Pisano, R. Lombardi, S. Spreafico, F. Iuculano, E. Fatta, V. Borroni, M. Porzio, S. Pelusi, L. Valenti, S. Fargion, A.L. Fracanzani

Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy

Introduction: Dietary macro-nutrient composition is associated with NAFLD, an inverse correlation between Mediterranean diet and cardiovascular events was reported. Aim to evaluate the role of dietary components on clinical presentation of NAFLD.

Methods: We enrolled 159 consecutive newly diagnosed, untreated NAFLD. A semi-quantitative food-frequency questionnaire (including 118 food items, covering seven days) administered at enrollment used to calculate energy and nutrients intake. Assessment of steatosis and subclinical atherosclerosis (mean carotid IMT and plaques) by B-mode ultrasound, cardiac diastolic dysfunction (E/A), left ventricular mass, epicardial adipose thickness (EAT), by echocardiography.

Results: The mean BMI and waist circumference were 28.8 ± 5.2 and 103 ± 11 cm, prevalence of hypertension 52%, dyslipidemia 56%, obesity 35%, diabetes 11%, metabolic syndrome 44%. Eighteen % had "lean" NAFLD (BMI <25). Mean IMT was 0.74 ± 0.2, carotid atherosclerosis (IMT >1.0 mm) in 14%, and plaques in 29%, E/A <1 in 40%, mean EAT 5.8 ± 4 mm. Eight patients (5%) had cardiovascular events. Macro-nutrient intake adjusted for percentage of calories was: proteins 23.1 ± 4, fat 33.1 ± 5, carbohydrates 38.5 ± 8, fiber 2.7 ± 1. No difference of nutrient dietary composition and total amount of calories between lean and overweight/obese patients. Among nutrients, fructose was significantly higher in patients with plaques ($p = 0.03$), vitamin E lower in patients with diastolic dysfunction ($p = 0.03$). At multivariate analysis adjusted for age, gender and BMI, fat resulted significantly associated with dyslipidemia (OR 1.2, 95%CI 1–1.4,$p = 0.04$), protein with hypertension (OR 1.23, 95%CI 1.02–1.5, $p = 0.03$), fat and carbohydrate with severe US steatosis (OR 1.3, 95%CI 1.1–1.5, $p = 0.002$ and OR 1.2, 95% CI 1.03–1.4, $p = 0.01$, respectively). No independent association was found between nutrients and subclinical atherosclerosis.

Conclusion: Nutritional intake does not differ between lean and overweight NAFLD suggesting a genetic predisposition to NAFLD in lean subjects. It remains to be defined the role of individual micro- and macro-nutrients on cardiovascular damage in NAFLD.

https://doi.org/10.1016/j.dld.2018.01.073

F-36

Screening of esophagogastric varices: Performance of the "Expanded Baveno VI criteria" and the "platelet 150/MELD 6" strategy in all etiology compensated advanced chronic liver disease

G. Tosetti [1], V. La Mura [1], R. D'Ambrosio [1], E. Degasperi [1], N. Mezzina [3], M. Viganò [3], M. Rumi [3], A.L. Fracanzani [4], R. Lombardo [4], M. Fraquelli [1], A. Aghemo [2], P. Lampertico [1], M. Primignani [1]

[1] *CRC "A. M. e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*
[2] *Humanitas University Department of Biomedical Sciences, Rozzano-Milan, Italy*
[3] *Liver Unit, Ospedale San Giuseppe, University of Milan, Milan, Italy*
[4] *Internal Medicine, Department of pathophysiology and Transplantation, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy*

Background: Baveno VI-criteria, i.e. liver stiffness measurement (LSM) <20 kPa and/or platelet (PLT) count >150,000/mm^3) in viral compensated advanced chronic liver disease (cACLD) allow sparing 20–25% variceal screening endoscopies. Recently, less conservative strategies to further reduce unneeded endoscopies ("Expanded-Baveno VI criteria": LSM <25 kPa and/or PLT >110,000/mm^3) were proposed. Due to the limits/unavailability worldwide of LSM a "PLT >150,000/MELD 6" strategy was also suggested.

Aim: To assess the accuracy of the "Expanded-Baveno VI criteria" and "PLT >150,000/MELD 6" strategies in a cohort of cACLD patients of any etiology, compared to the original "Baveno VI-criteria".

Methods: Compensated cirrhotic patients undergoing endoscopic variceal screening were evaluated. Laboratory data within 6 months and LSM within one year were retrospectively collected. Exclusion criteria: LSM unavailable/unsuccessful, previous decompensation, portal vein thrombosis, current or previous HCC and splenectomy.

Results: 471 of 1182 patients fulfilled inclusion criteria: 79% viral cACLD (316 HCV, 56 HBV), 21% metabolic/ETOH cACLD (ETOH 32, metabolic 50, mixed 17), PLT count 124 (36–347)/mm^3, LSM 19.1 kPa (7.7–75.0). 144 (31%) had varices; of these, 31 (21%) had varices requiring prophylaxis. Baveno VI criteria had 100% sensitivity (Se) and 100% negative predictive value (NPV) and 100 (21%) patients could have safely avoided endoscopy. "Expanded-Baveno VI" criteria maintain the same accuracy (Se 100% and NPV 100%) sparing 211 (45%) endoscopies ("Baveno VI-criteria" vs "expanded-Baveno VI" criteria $p < 0.001$, McNemar test). Conversely, the "PLT >150,000/MELD 6" strategy was less accurate (Se 90%; NPV 98,5%), since, similarly to the "expanded-Baveno VI criteria", could spare 41% endoscopies, but three of 31 patients with varices requiring prophylaxis (10%) would have lost.

Conclusions: "Expanded-Baveno VI" criteria are valid and reproducible in all etiologies cACLD and allow sparing up to 45% endoscopies without losing sensitivity. The "PLT >150,000/MELD 6" strategy is less accurate for ruling out patients for screening endoscopy.

https://doi.org/10.1016/j.dld.2018.01.074

F-37

Basal values and on treatment decline of hepatitis B core-related antigen are predictive of response to interferon therapy in patients with chronic hepatitis D

A. Olivero[1], G.P. Caviglia[1], A. Ciancio[1], C. Bosco[1], R. Fontana[2], G.A. Niro[2], M. Rizzetto[1], G.M. Saracco[1], A. Smedile[1]

[1] *Department of Medical Sciences, University of Turin, Turin, Italy*
[2] *Department of Gastroenterology, IRCCS Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy*

Introduction: Therapy with pegylated interferon-alpha-2a (Peg-IFN) is considered the standard-of-care for patients with chronic active HDV infection (CHD).

Aim: To investigate the role of hepatitis B core-related antigen (HBcrAg) for the prediction of response in CHD patients treated with Peg-IFN.

Materials and methods: Sixty-five serum samples from 13 CHD patients (8M/5F; median age 54 years) who underwent Peg-IFN treatment between 2010 and 2015 were analyzed. All patients were HBV genotype-D and HDV genotype-1; 11 were anti-HBe+. Serum HBcrAg and HBsAg levels were determined by CLEIA (Lumipulse®, Fujirebio, Japan); HBV DNA and HDV RNA by RT-qPCR. All markers were measured at baseline, 6, 12, 18 and 12 months after end of therapy (12 MFU).

Results: Overall, 8/13 patients cleared HDV RNA and were still negative at 12 MFU (responders, Rs). Among them, 2 patients cleared HBsAg and 1 became anti-HBs+. Five patients were non-responders (NRs). Mean baseline HBcrAg, HBsAg, HBV DNA and HDV RNA levels were 3.6 ± 1.4 LogU/mL, 3.17 ± 1.33 LogIU/mL, 2.02 ± 1.67 LogIU/mL and 4.79 ± 1.21 LogIU/mL, respectively. We observed a significant correlation between HBcrAg and HBsAg ($r = 0.763$, $p < 0.001$), HBV DNA ($r = 0.844$, $p < 0.001$) and HDV RNA ($r = 0.761$, $p < 0.001$). Baseline HBcrAg levels were slightly higher in NR compared to R patients (4.6 ± 1.3 vs. 3.1 ± 1.1 LogU/mL, $p = 0.052$). The area under the curve (AUC) for the discrimination between Rs and NRs was 0.787 (cut-off = 3 LogU/mL, sensitivity [Se] = 63% and specificity [Sp] = 80%). On-treatment HBcrAg kinetics showed a linear decline ($p = 0.026$) in R patients from baseline to 12 MFU; conversely, no decline was observed in NRs ($p = 0.256$). A 6M on treatment HBcrAg reduction >0.1 LogU/mL showed a AUC = 0.737 (Se = 88% and Sp = 60%). By combining baseline HBcrAg levels and reduction values at 6 months this accuracy improved (AUC = 0.925, Se = 100% and Sp = 80%).

Conclusions: Serum HBcrAg levels, at baseline and at month 6 on therapy, are predictors of treatment response to Peg-IFN in patients with CHD.

https://doi.org/10.1016/j.dld.2018.01.075

F-38

Direct-acting antiviral therapy immediately after liver transplant in naïve or NS5A-relapser recipients

S. Martini[1], C. Chialà[1], F. Calvo[1], F. Tandoi[2], D. Patrono[2], D. Cocchis[2], A. Ottobrelli[1], M. Salizzoni[2], G.M. Saracco[1], R. Romagnoli[2]

[1] *Gastrohepatology Unit, AOU Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy*
[2] *Liver Transplant Center and General Surgery 2U, AOU Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy*

Background and aims: Immediately post-liver transplant (LT), HCVRNA levels fall sharply and this period could represent a unique opportunity to cure infection. We aimed to evaluate efficacy and safety of preemptive direct-acting antiviral (DAA) therapy in naïve and NS5A-relapser LT recipients.

Method: Between 01/2016 and 05/2017, 63 adult HCV-positive cirrhotics underwent a first LT in our Centre, receiving a graft from brain-dead HCV-negative donor.

Immunosuppression: tacrolimus, mycophenolate mofetil and steroids.

Twenty recipients (32%) underwent preemptive DAAs (15 naïve to DAAs, received sofosbuvir + ledipasvir/daclatasvir ± ribavirin for 12 weeks; 5 relapsers to NS5A inhibitors, sofosbuvir + velpatasvir + ribavirin for 24 weeks), starting the day of LT, and represent our study population.

Clinical and virological outcomes were recorded until October 31, 2017.

Results:

Recipients: Median age 56 y, MELD at LT 12, HCC 60%, HCVRNA at LT 5.6 LogIU/mL; HCV genotype (GT) 1a: 5 patients; GT1b: 9 patients (1 relapser), GT3: 3 patients (1 relapser) and GT4 3 patients (all relapsers). Median LT waiting-list time: 10 days.

Donors: Median age 63 y; BMI 26 kg/m^2, 15% HBcAb positive, donor risk index 1.48, cold ischemia time 415 min.

Post-LT follow-up: Median hospitalization: 13 days, early allograft dysfunction according to Olthoff: 25%, 30-day treated acute cellular rejection: 10%.

All grafts and patients are alive after a median follow-up of 335 days, 1 patient with HCC recurrence at 10 months after-LT.

Within week-4 post-LT all patients were HCVRNA <15 IU/mL; all 15 DAA-naïve patients achieved a SVR12; the 5 NS5A relapsers are all negative at end of therapy, with 1 patient reaching SVR8 and 1 SVR12.

None discontinued DAA therapy post-LT.

Conclusions: In our 20 HCV-positive patients (15 naïve and 5 NS5A relapsers), preemptive DAA therapy was safe and well tolerated and HCVRNA <15 IU/mL was achieved within week-4 post-LT in all of them. The 16 patients who reached 12 weeks of follow-up after therapy, are SVR12.

https://doi.org/10.1016/j.dld.2018.01.076

F-39

Non-invasive evaluation of change in liver fibrosis after viral eradication in patients with HCV related cirrhosis

R. Carrara[1], A. Ferrarese[2], E. Franceschet[1], A. Zanetto[2], M. Gambato[2], A. Floreani[1], F. Farinati[1], P. Burra[2], F.P. Russo[1,2]

[1] *Gastroenterology, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy*
[2] *Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy*

Introduction: Novel direct acting antivirals (DAA) have significantly increased Hepatitis C (HCV) eradication in patients with cirrhosis; however, few data on the reduction of liver fibrosis after DAA therapy in cirrhotics are available.

Aim: To evaluate changes on liver fibrosis after DAA treatment in patients with HCV related cirrhosis.

Materials and methods: Between 03/2015 and 01/2017, all consecutive patients with cirrhosis who achieved sustained virological response (SVR) after treatment with DAAs were enrolled. Liver fibrosis was non-invasively assessed through Transient Elastography (TE, FibroScan) and AST/Platelet Ratio Index (APRI score), at DAA introduction and at SVR24 respectively.

Results: 87 patients with HCV related cirrhosis treated with DAA were prospectively enrolled; 9 (10.2%) patients were excluded (2 died, 3 underwent liver transplantation, 4 relapsed after EOT) and 78 (M/F 48/30, median age 57 years) were included in the final analysis. At SVR24, both albumin (39.7 [31–48] vs 42.6 [32–49] g/L, $p = 0.02$) and platelet count (112 [40–252] vs 142 [55–256] $\times 10^9$/L; $p = 0.02$) significantly increased than baseline; conversely serum bilirubin significantly decreased (15.4 [4–78] vs 11.6 [3–21] μmol/l, $p = 0.01$). At SVR24, TE values significantly decreased than baseline (20.9 [12–66] vs 14.5 [4–69] kPa; $p < 0.001$), and remained stable at SVR48 ($p = 0.8$). Similarly, APRI score values significantly decreased between baseline and SVR24 (1.3 [0.2–7.9] vs 0.5 [0.2–4.7]; $p < 0.001$) and remained stable thereafter ($p = 0.2$); after a median follow-up of 25.4 months (range 9–32), cumulative incidence of episodes of decompensation and HCC were 1.28% and 6.4%, respectively.

Conclusion: Achievement of SVR after DAA therapy improved liver function and determined a significant reduction in liver fibrosis measured by TE and APRI in a cohort of patients with cirrhosis.

https://doi.org/10.1016/j.dld.2018.01.077

F-40

Safety and effectiveness of DAA treatment and clinical outcomes of HCV liver transplanted patients with recurrent hepatitis C infection: A single center 3-year study from Italy

F. Invernizzi[1], M.F. Donato[1], S. Monico[1], M. Borghi[1], D. Dondossola[2], B. Antonelli[2], G. Lunghi[3], R. Perbellini[1], F. Fabrizi[4], G. Rossi[2], P. Lampertico[1]

[1] *CRC "A. M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy*
[2] *Hepatobiliary-pancreatic Surgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; Università degli Studi di Milano, Milan, Italy*
[3] *Division of Hygiene, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università di Milano, Milan, Italy*
[4] *Division of Nephrology and Dialysis, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università di Milano, Milan, Italy*

Background/aim: Hepatitis C virus (HCV) recurrence after liver transplantation (LT) was associated with a poor outcome until the introduction of DAAs. This study reports outcome of DAA treated recipients with HCV recurrent after LT.

Materials/methods: from May 2012 to January 2016, 125 HCV-RNA positive patients received DAAs (with/without IFN) 46 (0–268) months from LT: 78% a SOF-based regimen plus RBV, 6% SIM/DCV/RBV or 3D-regimen and 17% PEG-IFN/RBV plus Telaprevir or Sofosbuvir. At DAA-start, age was 61 years, 76% males, 71% HCV-1, 69% treatment-naïve, 48% transplanted for HCC, 58% on dual immunosuppression (CNI plus MMF), 75% arterial hypertension, 52% diabetes, 23% cirrhosis/FCH, 5 portal vein thrombosis, 42% eGFR <60 ml/min, median HCV-RNA level 1.890.231 UI/ml (14.588–51.491.894).

Results: Virological response was achieved in all patients (in 97% after the first therapy). DAA treatment was well tolerated; side effects: anaemia (erythropoietin support = 57 and blood transfusion = 15), asthenia and mild gastrointestinal disorders. After 10 months (3–18) from DAA-start, 8% patients showed liver graft dysfunction successfully treated by increasing immunosuppression. After a median follow-up of 26 months, liver stiffness declined from 11 to 7 kPa ($p < 0.05$); 4% developed de-novo portal thrombosis 30 months after DAA-starting; HCC recurred in 2 out of 60 HCC transplanted (month 2 and 13). Extra-hepatic cancer (renal, bladder) occurred in 2 patients (month 26 and 12). eGFR values did not significantly change (65 vs 63 ml/min) but 5 patients worsened kidney function (one required haemodialysis 8 months post-DAA; 3 had a nephrotic syndrome 9–20 months post-DAA). Overall, the 3-year cumulative incidence of hepatic and extrahepatic complications was 24%. The 3-year survival was 99%, only one patient died after 19 months due to sepsis related multi-organ failure.

Conclusions: DAA-treatment for HCV recurrence after LT is highly effective and safe. The 3-year survival was excellent but a quarter patients experienced extrahepatic complications.

https://doi.org/10.1016/j.dld.2018.01.078

Digestive and Liver Disease 50 (2018) 61

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

A.I.S.F. 2018: Abstracts evaluation procedure

Thanks to experts evaluating all the abstracts according to predetermined Clinical and Experimental categories.
The experts for the 2018 Annual Meeting are listed below:

Category B. **"HEPATITIS B & DELTA CLINICAL"**
B. Coco, Pisa - V. Di Marco, Palermo - C. Ferrari, Parma - A. Marzano, Turin – M. Masarone, Salerno - G. Taliani, Rome

Category C. **"HEPATITIS C CLINICAL"**
A. Aghemo, Milan - P. Andreone, Bologna - V. Di Marco, Palermo - A. Mangia, S.G. Rotondo (FG) - F. Morisco, Naples - G. Taliani, Rome - A.L. Zignego, Florence

Category D. **"NAFLD & ALD EXPERIMENTAL"**
A. Alisi, Rome - P. Dongiovanni, Milan - C. Loguercio, Naples

Category E. **"NAFLD & ALD CLINICAL"**
A. Fracanzani, Milan - C. Loguercio, Naples - C. Puoti, Grottaferrata (RM) - E. Vanni, Turin

Category F. **"AUTOIMMUNE HEPATITIS & BILIARY DISEASE"**
V. Cardinale, Rome - A. Floreani, Padua - L. Muratori, Bologna - C. Rigamonti, Novara - F. Rosina, Turin - C. Spirli, New Haven, CT (USA)

Category H. **"EXPERIMENTAL LIVER DAMAGE, FIBROSIS, CIRRHOSIS & PORTAL HYPERTENSION"**
M. Fraquelli, Milan - F. Marra, Florence – M. Parola, Turin - G. Svegliati-Baroni

Category I. **"FIBROSIS, CIRRHOSIS & PORTAL HYPERTENSION CLINICAL"**
F. Campagna, Padua - P. Caraceni, Bologna - V. La Mura, Milan - F. Schepis, Modena

Category L. **"HEPATOCELLULAR CARCINOMA EXPERIMENTAL"**
F. Farinati, Padua - G. Missale, Parma - E. Villa, Modena

Category M. **"HEPATOCELLULAR CARCINOMA CLINICAL"**
F. Farinati, Padua - M. Iavarone, Milan - G. Missale, Parma - F. Piscaglia, Bologna - G.L. Rapaccini, Rome - E. Villa, Modena

Category N. **"LIVER FAILURE, HEPATOBILIARY SURGERY & TRANSPLANTATION"**
M. Angelico, Rome - L. Baiocchi, Rome - P. Burra, Padua - M.F. Donato, Milan - S. Fagiuoli, Bergamo - E. Gringeri, Padua - M. Strazzabosco, Milan

Category O. **"MISCELLANEOUS: GENETIC, PEDIATRIC, NUTRACEUTICALS, DILI, OTHER"**
A. Cappon, Padua - S. Fargion, Milan - A. Gasbarrini, Rome – G. Germani, Padua – F. Giannone, Bologna - A. Lleo, Rozzano (MI) - G. Svegliati Baroni, Ancona

http://dx.doi.org/10.1016/j.dld.2018.01.130
1590-8658/