Towards Precision Medicine in Primary Biliary Cholangitis

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Il sottoscritto dichiara di non aver avuto negli ultimi 12 mesi conflitto d’interesse in relazione a questa presentazione e che la presentazione non contiene discussione di farmaci in studio o ad uso off-label.
Outline

• Background
• Current tools for risk stratification
  – Demographics
  – Liver biochemistry
  – Histology
  – Autoantibodies
  – Non invasive markers
• Potential future stratifiers
• How to develop precision medicine in PBC
Primary Biliary Cirrhosis

• **Definition** - Chronic, cholestatic liver disease characterized by non-suppurative granulomatous cholangitis; duct destruction and ductopenia, and portal fibrosis that progresses slowly to biliary cirrhosis.

• **Etiology** – Complex disorder, caused by a complex of largely unknown genetic and environmental factors. Putative autoimmune patogenesis

• **Diagnosis** - AMA and PBC-specific ANA in a patient with otherwise unexplained elevation of ALP is diagnostic of PBC. A liver biopsy is not essential for the diagnosis of PBC, except for seronegative PBC.
Primary Biliary Cholangitis

The rate of disease progression in PBC is highly variable.

UDCA is the only approved drug in Europe – however one third of patients do not respond – higher rate of morbidity and mortality

No targeted therapies currently available

No stratified approach is currently applied in clinical practice
# PBC is an heterogeneous disease

<table>
<thead>
<tr>
<th>Variant syndromes</th>
<th><em>PBC – AIH overlap syndrome</em> may be found in ~10% and the <em>premature ductopenic variant</em> in ~5% of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibody profile</td>
<td>Anti-centromere antibodies (ACA) are found in ~30%, anti-sp100 antibodies in ~20-30% and anti-gp210 antibodies in ~10% of cases</td>
</tr>
<tr>
<td>Symptom profile</td>
<td>Pruritus is present in 40% and fatigue is present in 45% of cases</td>
</tr>
<tr>
<td>Modes of disease progression</td>
<td><em>Portal hypertensive-type</em> versus <em>hepatocellular failure-type</em> progression</td>
</tr>
<tr>
<td>Rate of disease progression</td>
<td>Ranging from no overt progression at one end of the spectrum, to ESLD occurring within a few years of diagnosis, at the other</td>
</tr>
<tr>
<td>The biochemical response to UDCA</td>
<td>Variable; it strongly predicts the long-term outcome.</td>
</tr>
</tbody>
</table>
Stratification of Disease for Precision Medicine

RISK STRATIFICATION

• A systematic process for identifying and predicting patient’s risk level relating to the health care needs.
• Potentially useful to support personalized or precision medicine.

PRECISION MEDICINE

• Emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.
• Decisions regarding overall management are informed by an individual’s risk profile.
• Recognized as a key global priority with the ultimate goal being to offer ‘right treatment, for the right person, at the right time’

Hingorani AD et al. Prognosis research strategy (PROGRESS) 4: stratified medicine research. BMJ 2013 Feb
## Is risk stratification relevant in PBC?

**Unmet clinical needs in PBC**

<table>
<thead>
<tr>
<th>CHALLENGES IN PROGNOSIS</th>
<th>CHALLENGES IN CARE DELIVERY</th>
<th>CHALLENGES IN TRIAL DESIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarkers for high risk disease at diagnosis</td>
<td>Implementation of stratification criteria in practice enabling identification of high risk patients</td>
<td>Consensus stratification protocols to select high risk patients for second line therapy trials</td>
</tr>
<tr>
<td>Predictive markers of response to UDCA</td>
<td>Management location and approach for low risk patients</td>
<td>Surrogate markers of outcome as endpoints acceptable to regulatory bodies</td>
</tr>
</tbody>
</table>
STRATIFICATION FOR THE RISK OF ESLD

- Demographics
- Liver biochemistry
- Histology
- Autoantibodies
- Non-invasive markers
STRATIFICATION FOR THE RISK OF ESLD

<table>
<thead>
<tr>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver biochemistry</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Autoantibodies</td>
</tr>
<tr>
<td>Non-invasive markers</td>
</tr>
</tbody>
</table>
Gender differences in the age-related likelihood of achieving UDCA response criteria

Proportion of patients who did not meet the criteria for response to UDCA after a minimum of 2 years treatment because of the ALT/AST criterion (2 ULN) related to their age at diagnosis

Carbone M, Mells GF et al. Gastroenterology 2013
Predictors of survival – fatigue

Carbone M, Mells GF et al. Gastroenterology 2013

Jones DEJ et al. J Hepatol 2010
STRATIFICATION FOR THE RISK OF ESLD

Demographics

Liver biochemistry

Histology

Autoantibodies

Non-invasive markers
## Biochemical response criteria in UDCA-treated patients

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
<th>No patients</th>
<th>Evaluation time point</th>
<th>c-statistics at 5, 10, or 15 years *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barcelona, 2006</td>
<td>&gt;40% decrease of ALP or normalization</td>
<td>192</td>
<td>1 year</td>
<td>0.56, 0.61, 0.61</td>
</tr>
<tr>
<td>Paris I, 2008</td>
<td>ALP&lt;3xULN, AST&lt;2xULN and bilirubin≤1mg/dL</td>
<td>292</td>
<td>1 year</td>
<td>0.81, 0.81, 0.80</td>
</tr>
<tr>
<td>Rotterdam, 2009</td>
<td>Normalization of abnormal bilirubin and/or albumin</td>
<td>375</td>
<td>1 year</td>
<td>NA</td>
</tr>
<tr>
<td>Toronto, 2010</td>
<td>ALP ≤1.67xULN</td>
<td>69</td>
<td>2 year</td>
<td>0.65, 0.70, 0.70</td>
</tr>
<tr>
<td>Paris II, 2011</td>
<td>ALP≤1.5xULN, AST≤1.5xULN and bilirubins≤1mg/dL</td>
<td>165</td>
<td>1 year</td>
<td>0.75, 0.75, 0.74</td>
</tr>
<tr>
<td>Ehim, 2011</td>
<td>≥70% decrease of GGT</td>
<td>138</td>
<td>6 months</td>
<td>NA</td>
</tr>
</tbody>
</table>

* c-statistics calculated in the UK-PBC Research Cohort.
Current risk assessment in PBC

**UDCA response is a strong predictor of long-term survival**

- A. Barcelona criteria
- B. Paris I criteria
- C. Paris II criteria
- D. Toronto criterion

**AST/platelet ratio index predicts outcome independent of UDCA response**

Trivedi et al. – J Hepatol 2014

Pares A - Gastroenterology 2006
Kumagi T – Am J Gastro 2010
Corpechot C – Hepatology 2008
Corpechot C – J Hepatol 2011
Predictors of LT-free survival

Fitted lines derived from the best fitting multivariable fractional polynomial model

UK-PBC cohort

Cubic spline function
GLOBE cohort

Lammers et al. Gastroenterology 2014
The PBC Risk Scores

Algorithm = 1-baseline survival function^exp(.0287854*(alp12-xuln-1.722136304) .0422873 * (((altast12xuln/10)^-1)28.675729006) 11.4199*(ln(bil12xuln/10) 12.709607778)21.960303*(albxlln-1.17673001)-.4161954*(pltxlln-1.873564875))

Baseline survivor function: 0.982 (at 5 years); 0.941 (at 10 years); 0.893 (at 15 years)

- **Tool for disease management** to identify high-risk patients for closer monitoring and second-line therapies, as well as low-risk patients who require infrequent monitoring and might even be followed-up in primary care.

- **Stratification of patients in clinical trials**

- **Surrogate endpoint measure in clinical trials**
STRATIFICATION FOR THE RISK OF ESLD

Demographics
Liver biochemistry
**Histology**
Autoantibodies
Non-invasive markers
Histological stage

Plot of survivor function of ALP and Ludwig stage

Adjusted for age, sex, year of diagnosis

(n=510)

Carbone M & Mells GF - Unpublished data
Interface hepatitis

Cox proportional hazards regression

Adjusted for age, sex, year of diagnosis

No IH
Focal IE
Widespread IE
No IE
Focal IH
Widespread IH

Responders (Paris 1)
Non responders (Paris 1)

Carbone M & Mells GF - Unpublished data
Ductopenia

- Retrospective analysis of PBC patients with follow-up liver biopsy 10 years after initial histologic diagnosis (N=69).

- Patients who did not respond to UDCA were more likely to have ductopaenia (>50% bile duct loss) on pre-treatment biopsy (p=0.02).

- Cutoff of BD loss to predict non response= <45.8% (p<0.001)

Kumagi T et al. Am J Gastro 2010
STRATIFICATION FOR THE RISK OF ESLD

- Demographics
- Liver biochemistry
- Histology
- Autoantibodies
- Non-invasive markers
PBC-specific anti-nuclear antibodies

• **AMA** - no prognostic value
  - Carbone M, Mells GF et al. Gastro 2013
  - Lammers W et al. Gastro 2014

• **Anti-gp210** - 6-fold risk of progression to liver failure/transplantation

• **Anti-centromere antibodies** - associate with PH
Anti gp210


STRATIFICATION FOR THE RISK OF ESLD

- Demographics
- Liver biochemistry
- Histology
- Autoantibodies

Non-invasive markers
Non-invasive markers

### VCTE

**Precedents:**
- Increased risk of clinical events (decompensation, LT, and liver-related mortality) independent of biochemical response in patients with LSM >9.6 kPa, or ΔLSM >2.1 kPa/yr\(^7\)

**Studied cohorts:**
- n = 150; single-center and UDCA treated

**Comment:**
- Proven surrogate of fibrosis in PBC. However, validation as an outcome predictor pending
- Unclear whether adds predictive value to biochemical response status

### ELF

**Precedents:**
- Significant differences in clinical event rate between score tertiles\(^7\)
- Δ1-point increase imparts 3-fold greater risk of liver-related events

**Studied cohorts:**
- n = 161; multicenter national data extrapolated from a clinical trial of methotrexate and UDCA

**Comment:**
- Unclear whether adds predictive value to biochemical response status
- Impact of longitudinal stability vs. fluctuations over time yet to be determined
- Not yet validated
- Unclear whether stratifier of disease severity vs. stage

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Corpechot et al. Hepatology 2012

Mayo M et al. Hepatology 2009
NOVEL POTENTIAL STRATIFIERS

Genetics
Transcriptomics
Metabolomics
Proteomics
Lipidomics
Microbiota
SNPs at 6 loci achieved $P_{\text{DISCOVERY}} < 5 \times 10^{-6}$
Of these, none identified in GWAS of susceptibility of PBC

Deviation in the tail of the distribution is suggestive of true associations

<table>
<thead>
<tr>
<th>CHR</th>
<th>SNP</th>
<th>A1</th>
<th>EST</th>
<th>SE</th>
<th>P-value</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>7p22</td>
<td>rs12666575</td>
<td>G</td>
<td>0.38</td>
<td>0.07</td>
<td>$1.32 \times 10^{-07}$</td>
<td>MAD1L1,MIR4655,FTSJ2,NUDT1,SNX8</td>
</tr>
<tr>
<td>7q31</td>
<td>rs4727713</td>
<td>G</td>
<td>0.53</td>
<td>0.12</td>
<td>$8.93 \times 10^{-06}$</td>
<td>NRCAM,PNPLA8,RPL7P32,THAP5,DNAJB9</td>
</tr>
<tr>
<td>8p22</td>
<td>rs1378029</td>
<td>A</td>
<td>0.34</td>
<td>0.07</td>
<td>$2.79 \times 10^{-06}$</td>
<td>SGCZ</td>
</tr>
<tr>
<td>8q21.3</td>
<td>rs10429299</td>
<td>A</td>
<td>0.39</td>
<td>0.08</td>
<td>$7.12 \times 10^{-07}$</td>
<td>SOX5P,LOC100419762,DCAF4L2,MMP16</td>
</tr>
<tr>
<td>11p15.5</td>
<td>rs1004446</td>
<td>G</td>
<td>-0.35</td>
<td>0.08</td>
<td>$4.76 \times 10^{-06}$</td>
<td>INS-IGF2,IGF2, MIR483,IGF2-AS,INS,TH,MIR4686</td>
</tr>
<tr>
<td>12q22-23</td>
<td>rs34580</td>
<td>A</td>
<td>0.45</td>
<td>0.09</td>
<td>$1.91 \times 10^{-06}$</td>
<td>Intergenic</td>
</tr>
</tbody>
</table>
Metabolomics

Bell et al. Liver Int 2015
The time is ripe for precision medicine

• Rapid advances and decreased costs of omics technology and monitoring devices

• Information technology platforms

• Agencies are interested in more targeted approach

• Patients will be engaged in research that will benefit them, not the next generation
Key components to develop Stratified and Precision Medicine in PBC
1. A large research cohort

Necessary to identify sufficient number of cases for well-powered sub-phenotype analyses. Larger collections with international collaborations.
2. Extensive clinical characterization
This is necessary to identify and re-define known sub-phenotypes (and hitherto unknown sub-phenotypes) within the research cohort.

3. Sampling of diverse biofluids or tissues
To enable high-throughput analysis of relevant biofluids or tissue samples (DNA, serum, plasma, PBMCs, urine, stool and liver).

Time for one-person trials
Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says Nicholas J. Schork.
4. Genotyping and/or deep phenotyping
Improved genotyping and phenotyping and molecular stratification.

5. Drug development and/or re-purposing
Aim is to identify previously unknown targets for pharmacological intervention, guiding the development or re-purposing of targeted therapies.
Summary

- PBC is heterogeneous in its presentation, treatment response and disease progression.
- Up to 30% of patients have an incomplete response to UDCA and higher risk of predictor of poor outcome – unmet need.
- The rise of data-intensive biology, advances in information technology and the availability of large-scale cohort offer a unique opportunity for developing a stratified and precision medicine in the field.
Thank you
Disease-stage based approach to novel PBC therapeutics
## Active and recently run clinical trials in PBC

<table>
<thead>
<tr>
<th><strong>DRUG NAME</strong></th>
<th><strong>CLASS OF DRUG</strong></th>
<th><strong>RATIONALE</strong></th>
<th><strong>PHASE OF DEVELOPMENT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>INT 767</td>
<td>TGR5 agonists</td>
<td>Dual FXR and TGR5 agonist shown to affect energy metabolism, glucose homeostasis, bile composition/secretion, and inflammation.</td>
<td>Phase 1 (recruiting)</td>
</tr>
<tr>
<td>FFP104</td>
<td>Anti-CD40</td>
<td>CD 40 plays a key role in CD4 (^+) T-cell priming, B-cell terminal maturation, and immunoglobulin (Ig) class-switch recombination. Administration of anti-CD40L in murine models of autoimmune cholangitis reduces liver inflammation significantly lowers the levels of AMA.</td>
<td>Phase 1-2 (recruiting)</td>
</tr>
<tr>
<td>Bezafibrate, Fenofibrate</td>
<td>PPAR-α</td>
<td>Improvement of hepatic inflammation through PPARα and MDR3</td>
<td>Phase 2 (recruiting)</td>
</tr>
<tr>
<td>MBX-8025</td>
<td>PPAR - Y</td>
<td>Activation of PPAR - Y in stellate cells reverse their activation and might be involved in fibrosis regression.</td>
<td>Phase 2 (recruiting)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Anti-CD20</td>
<td>B-cell depleting therapy shown to reduced fatigue in pilot study in PBC (^-). Endpoint is reduction of fatigue.</td>
<td>Phase 2 (active)</td>
</tr>
<tr>
<td>Lopixibat</td>
<td>ASBT inhibitors</td>
<td>Apical sodium-dependent bile acid transporter inhibitor reduces bile acid accumulation in the liver. Trial endpoint is reduction of pruritus.</td>
<td>Phase 2 (closed)</td>
</tr>
<tr>
<td>NI-0801</td>
<td>Anti-CXCL-10</td>
<td>The chemokine CXCL10 plays an important role in T cell trafficking by binding CXCR3, highly expressed on effector T cells, that drives infiltration of inflammatory lymphocytes into the liver.</td>
<td>Phase 2 (closed)</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Anti-IL12/IL23</td>
<td>Blockade of IL12/23 pathway, key player in the effector mechanisms that lead to biliary destruction, could alleviate inflammation in PBC.</td>
<td>Phase 2 (closed)</td>
</tr>
<tr>
<td>Obeticholic Acid (OCA)</td>
<td>FXR agonists</td>
<td>Bile acid shown anti-cholestatic, anti-inflammatory, and anti-fibrotic effects in clinical studies, through the activation of the FXR</td>
<td>FDA filing Phase 3 (confirmatory trial, recruiting)</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Chimeric CTLA4</td>
<td>Fusion protein of the extracellular domain of CTLA-4 and human IgG1, which binds to CD80 and CD86 molecules on the APC and prevents the co-stimulatory signal being delivered to the T cell that is needed for an immune response.</td>
<td>Phase 4 (recruiting)</td>
</tr>
</tbody>
</table>
Big hopes for big data

Technology is allowing researchers to generate vast amounts of information about tumours. The next step is to use this genomic data to transform patient care.

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says Nicholas J. Schork.
Moving forward with precision medicine

• The idea of deep phenotyping has been suggested as a way to improve precision medicine
• these phenotypic characteristics would need to include assessment of the expression and function of the many mediators that can influence hepatic and extrahepatic drug metabolism and transport.
• These assessments can be particularly challenging in patient populations given the diversity in drug substrates and the complex overlap in substrate specificity among the drug metabolism enzymes and membrane transporters.
• This clearly shows that, in addition to the need for reliable diagnosis of NASH, the ADME phenotype of liver diseases needs to be determined for accurate translation of clinical observations into recommendations for precision medicine.
È molto più importante sapere quale tipo di paziente ha una malattia che quale malattia ha un paziente

William Osler

Thanks