Clinical Management of viral hepatitis in dialysis

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Topics to be covered

- Epidemiological and clinical characteristics
- Adverse impact on survival of HCV
- Main renal manifestation of HCV and diagnosis
- Therapeutical regimen
- HBV related infection
Epidemiology of HCV infection in haemodialysis

Jadoul M et al, Nephrol Dial Transplant, 2004
European study on epidemiology and management of hepatitis C virus infection in the haemodialysis population

Zampieron A et al EDTNA/ERCA Journal 2006
Peritoneal dialysis

HD equipment contamination

Breakdown in infection control practices

A.D e.v
Clots factors and hemoderivates (before 1987)

Blood Transfusion (before 1992)

Increasing rates of HCV positive pts

Peritoneal dialysis
HD equipment contamination
HCV Transmission in haemodialysis units: recognized causes

- Nosocomial Spread
- Dialyzer reuse
- Internal contamination of dialysis machines
- Contamination of staff members and patients in dialysis
- Items shared between patients
- Asymptomatic seroconversion

CDC: recommendations for preventing transmission of infections among chronic hemodialysis patients 2004 Guidelines EDTNA ERCA J, 2006
Predisposing factors for “de novo” HCV infection

- Long time on HD
- Receiving HD treatment on multiple different centers
- Receiving HD treatment on centers with high prevalence of HCV
- Positive history blood of transfusion before 1990
- Previous RT
HCV and ESRD: Natural History

- ESRD
  - Liver-related Mortality (Cirrhosis, HCC)
  - Infections

- RT
  - Reduction of Patient and Graft Survival

Meta-analysis
Fabrizi et al, Aliment Pharmacol Ther 2004

Manga Sahin et al, 2006
Transplantation Proceedings

Courtesy of Prof. Smedile
Impact of HCV infection in survival

Scott DR et al Transplantation 2010

23,046 pts on dialysis
HCV Ab+ vs Ab-ve
45% vs 47% 5 yrs survival
22% vs 20% 10 yrs survival
aHR for mortality 1.25 (95% CI 1.07-1.46)
Liver failure more likely
outcome slightly worse for HCV Ab+ve pts on dialysis

## Effect of HCV infection on mortality

Anti-HCV positive vs negative pts aRR for all the mortality causes

<table>
<thead>
<tr>
<th>Autore</th>
<th>N° di pazienti</th>
<th>Paese</th>
<th>aRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pereira (1998)</em></td>
<td>496</td>
<td>USA</td>
<td>1.41</td>
<td>1.01-1.97</td>
</tr>
<tr>
<td><em>Stehman-Breen (1998)</em></td>
<td>200</td>
<td>USA</td>
<td>1.97</td>
<td>1.16-3.33</td>
</tr>
<tr>
<td><em>Nakayama (2000)</em></td>
<td>1470</td>
<td>Japan</td>
<td>1.57</td>
<td>1.23-2.00</td>
</tr>
<tr>
<td><em>Espinosa (2001)</em></td>
<td>175</td>
<td>Spain</td>
<td>1.62</td>
<td>1.05-2.49</td>
</tr>
<tr>
<td><em>DA Godkin (2003)</em></td>
<td>305</td>
<td>USA, EU, Japan</td>
<td>1.17</td>
<td>-</td>
</tr>
</tbody>
</table>

*aRR: adjusted relative risk (Cox proportional hazard)*
## Causes of Death in Anti-HCV positive RT Followed for $\geq 10$ years

<table>
<thead>
<tr>
<th>Authors, yr</th>
<th>No. of deaths</th>
<th>Cardiovascular (%)</th>
<th>Infection (%)</th>
<th>Liver (%)</th>
<th>Neoplasia (%)</th>
<th>Others (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathurin, 1999</td>
<td>38</td>
<td>16</td>
<td>18</td>
<td>21</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>Gentil, 1999</td>
<td>13</td>
<td>39</td>
<td>31</td>
<td>15</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Aroldi, 1998</td>
<td>19</td>
<td>47</td>
<td>32</td>
<td>21</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Legendre, 1998</td>
<td>15</td>
<td>-</td>
<td>27</td>
<td>40</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Hanafusa, 1998</td>
<td>18</td>
<td>11</td>
<td>28</td>
<td>28</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Overall</td>
<td>103</td>
<td>21%</td>
<td>25%</td>
<td>24%</td>
<td>10%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Post-transplant outcome in patients with pre-transplant HCV infection

Liver
- Greater incidence of increase of transaminases
- Fibrosing cholestatic hepatitis
- Increased viral replication

Extrahepatic
- NODAT
- Sepsis

Kidney
- Glomerulonephritis membranoproliferative with or without cryoglobulinemia
- Acute and chronic transplant glomerulopathy
- Renal thrombotic microangiopathy

Adapted from Morales JM, Transplantation Proceedings 2004
<table>
<thead>
<tr>
<th>Author, Country, Year</th>
<th>N.</th>
<th>Test determining HCV status</th>
<th>Mean FU mos</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pereira'98 USA</td>
<td>111 HCV+ kidney recipient</td>
<td>EIA 3</td>
<td>73</td>
<td>transplant vs dialysis</td>
</tr>
<tr>
<td></td>
<td>112 HCV+ pts on waiting list</td>
<td></td>
<td>7-47 mos after</td>
<td>aRR 0.3</td>
</tr>
<tr>
<td>Bloom 2005 USA</td>
<td>138 HCV+ kidney recipients</td>
<td>EIA 2 3</td>
<td>48</td>
<td>transplant vs no</td>
</tr>
<tr>
<td></td>
<td>117 HCV+ pts on waiting list</td>
<td></td>
<td></td>
<td>(20 vs 50%)</td>
</tr>
<tr>
<td>Knoll ‘97 USA</td>
<td>33 HCV+ kidney recipient</td>
<td>EIA 1</td>
<td>39</td>
<td>transplant vs dialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(15 vs 30%)</td>
</tr>
</tbody>
</table>

KDIGO guidelines 2008
NATURAL HISTORY OF HCV IN DIALYSIS PATIENTS

Fabrizi, 1997; Guh, 1995; Umlauft, 1997

An indolent course:

• ALT values lower than in the non uremic population
• HCV-RNA levels 1-3 log lower
• intermittent viremia
• viremic pts may have normal ALT values

….but in 60-70% of patients moderate to severe liver damage !!!
PATIENTS ON HAEMODIALYSIS EVALUATION ACCORDING TO HCV PREVALENCE

 CKD Stage 5 HD

 Admission to HD facility
 Transfer from other HD facility
 Testing every 6-12 months

 HCV test

 Low-prevalence setting

 EIA

 (+)

 (-)

 Normal

 ALT/AST

 Abnormal

 High-prevalence setting

 NAT

 (-)

 (+)

 If HCV outbreak
 Repeat NAT in 2-12 weeks

 Consider antiviral TX

 KDIGO Clinical Practice Guidelines 2008
Early diagnosis for “de novo” HCV infection

- Anti-HCV Elisa at the start of dialysis/transfer from another haemodialysis facility (window period 68 days)
- RT-HCV-RNA quantitative assays (10-30 IU/ml)
- TMA for qualitative assessment of HCV RNA (10 IU/ml)
Follow up of patients HCV negative in haemodialysis

- Vaccination for hepatitis A and B
- Monitor ALT every month
- Biannual monitoring of HCV RNA
- Screening of HCV Ab every 6-12 mos unless ALT levels increase
Liver biopsy in patients with CKD

- Liver biopsy not without risk
- Drugs with anti-PLT activity and uremic PLT dysfunctions increase this risk
- Liver biopsy before kidney transplantation regardless of HCV genotype
  - to determine the severity of hepatic injury
  - to assess prognosis and management of pt before and after transplant

KDIGO guidelines 2008
Diagnostic role of non invasive assessment of fibrosis: preliminary data

- FibroTest: 20% PPV for scores >0.6 and 45% NPV for score <0.2
  
  Canbakan M et al Nephron Clin Pract 2011

- Fibroscan was compared to LB in 242 HD pts with CHC. The NPV and PPV for fibrosis ≥2 were 96% for cut-off levels of 6 kPa

  Liu et al Hepatol Int 2010
HCV TX in Dialysis
Antiviral therapy: who should be treated

- Patients with long life expectancy
- Patients with short life expectancy only in case of advanced liver damage
- Patients with easy to treat genotype
- All the pts candidating for RT

KDIGO guidelines 2008
# PEG-IFN monotherapy in hemodialysis patients with chronic hepatitis C

*studies published between 2006-2010*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Pts</th>
<th>HCV 1</th>
<th>PEG-IFN</th>
<th>Dosage</th>
<th>Wks</th>
<th>Drop-outs</th>
<th>SVR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russo 2006</td>
<td>16</td>
<td>15</td>
<td>α-2b</td>
<td>0.5-1 µg/Kg</td>
<td>24</td>
<td>43%</td>
<td>12.5</td>
</tr>
<tr>
<td>Casanovas 2007</td>
<td>12</td>
<td>7</td>
<td>α-2a</td>
<td>135 µg</td>
<td>48</td>
<td>33%</td>
<td>25</td>
</tr>
<tr>
<td>Amarapukar 2007</td>
<td>6</td>
<td>1</td>
<td>α-2b</td>
<td>1 µg/Kg</td>
<td>24</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Espinosa 2007</td>
<td>10</td>
<td>uk</td>
<td>α-2a/2b</td>
<td>135 µg-1.5 µg</td>
<td>48</td>
<td>28%,44%</td>
<td>25</td>
</tr>
<tr>
<td>Liu 2008</td>
<td>25</td>
<td>20</td>
<td>α-2a</td>
<td>135 µg</td>
<td>24</td>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>Akhan 2008</td>
<td>12</td>
<td>12</td>
<td>α-2b</td>
<td>0.5 -1 µg/Kg</td>
<td>24</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Ayaz 2008</td>
<td>22</td>
<td>22</td>
<td>α-2b</td>
<td>135 µg</td>
<td>24</td>
<td>23%</td>
<td>50</td>
</tr>
<tr>
<td>Sikole 2008</td>
<td>14</td>
<td>13</td>
<td>α-2a</td>
<td>135 µg</td>
<td>48</td>
<td>42%</td>
<td>42</td>
</tr>
<tr>
<td>Alsaran 2010</td>
<td>13</td>
<td>13</td>
<td>α-2a</td>
<td>135 µg</td>
<td>48</td>
<td>0</td>
<td>69</td>
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</tbody>
</table>
α-IFN and ribavirin in haemodialysis patients with chronic hepatitis C

- Small number of patients in pilot studies
- Low doses of Ribavirin
- Severe anemia
- High doses of erythropoietin (20,000-30,000 IU/week)
### PEG-IFN + RBV therapy in haemodialysis patients with CHC

*Studies published between 2006-2010*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Pts</th>
<th>HCV</th>
<th>PEG-IFN</th>
<th>Dosage of RBV</th>
<th>Wks</th>
<th>Drop-outs</th>
<th>SVR (%)</th>
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</thead>
<tbody>
<tr>
<td>Bruchfeld 2006</td>
<td>6</td>
<td>5</td>
<td>α-2b</td>
<td>170-300 mg/die</td>
<td>24/48</td>
<td>33%</td>
<td>16</td>
</tr>
<tr>
<td>Rendina 2007</td>
<td>35</td>
<td>16</td>
<td>α-2a</td>
<td>200 mg/die</td>
<td>24/48</td>
<td>11%</td>
<td>97</td>
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<tr>
<td>Van Leusen 2008</td>
<td>14</td>
<td>4</td>
<td>α-2a</td>
<td>130-200 mg/die</td>
<td>24/48</td>
<td>uk</td>
<td>71</td>
</tr>
<tr>
<td>Carriero 2008</td>
<td>14</td>
<td>12</td>
<td>α-2a</td>
<td>200 mg/die</td>
<td>24/48</td>
<td>71%</td>
<td>28</td>
</tr>
<tr>
<td>Hakim 2009</td>
<td>15</td>
<td>18</td>
<td>α-2a</td>
<td>200 mg x 3 weekly</td>
<td>48</td>
<td>67%</td>
<td>5</td>
</tr>
<tr>
<td>Liu 2009</td>
<td>35</td>
<td>25</td>
<td>α-2a</td>
<td>200 mg x 3 weekly</td>
<td>24/48</td>
<td>17%</td>
<td>60</td>
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</table>
### Antiviral Tx in HCV+ve pts depending upon GFR

<table>
<thead>
<tr>
<th>Degree of renal dysfunction</th>
<th>Recommendation</th>
<th>Interferon dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR &gt;50 ml/min/1.73m²</td>
<td>As on HCV+ pts without kidney disease</td>
<td>Peg-IFNα/wk 2a 180 mcg, 2b 1.5 mcg/Kg+ RBV 800-1400 mg/die</td>
</tr>
<tr>
<td>GFR 15-50 ml/min/1.73m²</td>
<td>Monotx with Peg-IFN (adjusted doses). RBV administration strictly controlled. EPO given</td>
<td>Peg-IFNα/wk 2a 135 mcg, 2b 1 mcg/Kg± RBV 200-300 mg/die</td>
</tr>
<tr>
<td>GFR&lt;15 ml/min/1.73m²</td>
<td>Monotx only with std IFN or Peg-IFN on adjusted doses</td>
<td>IFN 3 MU x 3/ wk or PegIFN 2a 135 mcg 2b 1 mcg/Kg</td>
</tr>
</tbody>
</table>
Hepatitis B virus
Epidemiology of HBV infection in hemodialysis

- In Western Europe and USA the frequency of chronic HBsAg carriers ranges from 0% to 7%.
- In 78% of facilities the seroconversion rate is 0%.
- Outbreaks of HBV infection, however, continue to occur.

Burdick RA et al (DOOPS Study), Kidney Intern 2003)
Lamivudine in Active HBsAg+ve carriers on dialysis

<table>
<thead>
<tr>
<th>reference</th>
<th>pts</th>
<th>follow-up</th>
<th>HBeAg clearance</th>
<th>HBV DNA clearance</th>
<th>Lam-resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fontaine 2005</td>
<td>5</td>
<td>12</td>
<td>1(20)</td>
<td>5(100)</td>
<td>2(40)</td>
</tr>
<tr>
<td>Be-Ari 2000</td>
<td>6</td>
<td>14.4</td>
<td>3(50)</td>
<td>5(83)</td>
<td>1(7)</td>
</tr>
<tr>
<td>Boyacioglu 2002</td>
<td>7</td>
<td>NA</td>
<td>3(100)</td>
<td>7(100)</td>
<td>0</td>
</tr>
<tr>
<td>Schmilovitz-Weiss 2003</td>
<td>4</td>
<td>10</td>
<td>4(100)</td>
<td>4(100)</td>
<td>0</td>
</tr>
<tr>
<td>Lapinski 2005</td>
<td>16</td>
<td>12</td>
<td>6(38)</td>
<td>8(56)</td>
<td>0</td>
</tr>
</tbody>
</table>

Fabrizi F et al 2008
<table>
<thead>
<tr>
<th>Degree of renal dysfunction</th>
<th>Recommendation</th>
<th>NAA dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR &gt;50 ml/min/1.73m²</td>
<td>As on HBV+ pts without kidney disease</td>
<td>Entecavir 0.5-1 mg Tenofovir 300 mg</td>
</tr>
<tr>
<td>GFR 15-50 ml/min/1.73m²</td>
<td>High genetic barrier drugs</td>
<td>Use half dose of tenofovir</td>
</tr>
<tr>
<td>GFR&lt;15 ml/min/1.73m²</td>
<td>Avoid Tenofovir</td>
<td>Half dose of entecavir or prolonged interval between doses</td>
</tr>
</tbody>
</table>
HCV/HBV and ESRD
Take home messages I

• Prevalence and Incidence of **HCV** in ESRD is on the decline in Italy (AISF Commission Update 2006)

• Maintain control and application of general measures to prevent **HCV de novo** in the haemodialysis units

• Implement HCV Diagnosis and monitoring by molecular biology assays
HCV/HBV and ESRD
Take home messages II

- Evaluate non-invasive procedures for liver disease diagnosis

- Controlled Trials with IFN- Peg/IFN-Peg+Ribavirin are needed before RT to improve post-transplant prognosis

- The risk of HBV infection is low

- Only active HBsAg carriers should be treated and treatment adjusted on the basis of GFR