Use of HCV+ donors

Didier Samuel
Centre Hépato-Biliaire
Hôpital Paul Brousse, Villejuif, France
Dealing with organ shortage

- Despite concerted efforts to safely expand the donor organ pool, there is a widening gap between organ availability and demand.

Activity of liver transplantation in France
Anti-HCV+ liver grafts represent an important resource

- Worldwide, an estimated 130–170 million people have HCV infection
- Prevalence of HCV differs dramatically between regions

344 identified HCVD+ in France from 2006 to 2013

- The seroprevalence of HCV is higher in donors compared to overall population
- In a US collaborative study, the prevalence of anti-HCV positive donors was 5.6%, higher in high risk donors
- In France, 1.4% of donors

56 were harvested for at least one organ

- 35 Kidneys
- 36 Livers

16% Age
Quality of the graft
No available recipients!

1. Ellingson, K. AJT. 2011; 2. French Agency Data
The dilemma using anti-HCV+ liver grafts

✓ Risk of transmission
  • Variable depending on viral replication, HCV status of the recipient

✓ Benefits for the recipients
  • Emergency of the liver transplantation
How to optimize the use of anti-HCV+ liver grafts?

- Minimizing risks
- Maximizing benefits
  - Selection of donors/recipient
  - Controlling the risk
  - Effective prophylaxis or treatment
Selection of anti-HCV+ donors/recipient

☑ All donors are currently screened for HCV status
  • ELISA testing is the gold standard (Se>99%)

☑ Anti-HCV+ donors should be screened for
  • HCV RNA positivity in sera (NAT): availability?
  • Liver fibrosis (<F2)

  • Only 53% to 57% have active viral replication compared to approximately 60–80% of anti-HCV-positive individuals\textsuperscript{1-3}

☑ Anti-HCV+ liver grafts are allocated to patients who consent to receive such organs and who have a HCV+ status

Transmission to recipients with negative HCV RNA

- **Risk of transmission**
  - **Kidney**
    - 48%
  - **Heart**
    - 25%
  - **Liver**
    - No Replication: 0%
    - Replication: 100%

- Recipients with a positive serology but with an undetectable HCV RNA have theoretically a similar exposure risk than naive patients, as there is no protective cross-immunity between different inocula of HCV

Only one strain dominates after liver transplantation. In a detailed genetic analysis, strain of donor or recipient were found in 50\%\(^1\)

The dominance is not related to donor or recipient status but genotype\(^2\)

In 23 liver recipients, patients in whom the donor strain became predominant had significantly longer disease-free survival than patients who retained their own HCV strain\(^3\)

| Donor Genotype | Recipient Pre-genotype | Recipient Pre-RNA | Recipient Post-genotype | Recipient Post-
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>RNA</td>
<td>RNA</td>
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<td>RNA</td>
<td>RNA</td>
</tr>
<tr>
<td>A</td>
<td>1a 93 300</td>
<td>1b 25 300</td>
<td>1a 10 300</td>
<td>000</td>
</tr>
<tr>
<td>B</td>
<td>1b 1 100 000</td>
<td>1a 1 040 000</td>
<td>1a &gt;700 000</td>
<td>000</td>
</tr>
<tr>
<td>3</td>
<td>1a 91 800</td>
<td>1b 148 000</td>
<td>1b 18 700</td>
<td>000</td>
</tr>
<tr>
<td>4</td>
<td>1a 4 140 000</td>
<td>2b 82 400</td>
<td>1a 23 400</td>
<td>000</td>
</tr>
<tr>
<td>5</td>
<td>1b 6 630 000</td>
<td>3a 321 000</td>
<td>1b 626 000</td>
<td>000</td>
</tr>
<tr>
<td>6</td>
<td>2b 5 560 000</td>
<td>1b 1 730 000</td>
<td>1b 930 000</td>
<td>000</td>
</tr>
<tr>
<td>7</td>
<td>2b 19 700 000</td>
<td>1b 20 400</td>
<td>1b &gt;69 000 000</td>
<td>000</td>
</tr>
<tr>
<td>8</td>
<td>1b 12 100 000</td>
<td>3a 822 000</td>
<td>1b &amp; 3a 28 400 000</td>
<td>000</td>
</tr>
<tr>
<td>9</td>
<td>2b 8 200 000</td>
<td>1a 448 2</td>
<td>17 200 000</td>
<td>000</td>
</tr>
</tbody>
</table>

Bold genotypes dominate.

## Outcome after liver transplantation

<table>
<thead>
<tr>
<th>First author (Ref.)</th>
<th>Study period</th>
<th>Method</th>
<th>Number of HCVD+ (HCV RNA+)</th>
<th>Impact on patient survival/rate</th>
<th>Impact on graft survival</th>
<th>Impact on HCV recurrence</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballarin R [13]</td>
<td>1999-2009</td>
<td>Multicenter case-control study</td>
<td>63 (27)</td>
<td>No 61.7% at 5 years</td>
<td>No</td>
<td>Faster (non-significant)</td>
<td>&gt;5 years</td>
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<tr>
<td>Vargas HE [21]</td>
<td>1992-1995</td>
<td>Retrospective single-center study</td>
<td>23 (n.a.)</td>
<td>No 75% at 1 year</td>
<td>No</td>
<td>Less severe recurrence</td>
<td>5 years</td>
</tr>
<tr>
<td>Torres M [25]</td>
<td>1994-1998</td>
<td>Retrospective single-center study</td>
<td>8 (n.a.)</td>
<td>No 90% at 2 years</td>
<td>n.a.</td>
<td>n.a.</td>
<td>3 years</td>
</tr>
<tr>
<td>Marroquin CE [27]</td>
<td>1994-1997</td>
<td>Register and comparative study</td>
<td>96 (n.a.)</td>
<td>No 69% at 5 years</td>
<td>n.a.</td>
<td>n.a.</td>
<td>2 years</td>
</tr>
<tr>
<td>Velidedeoglu E [28]</td>
<td>1995-1999</td>
<td>Register and comparative study</td>
<td>190 (n.a.)</td>
<td>No 69% at 5 years</td>
<td>No</td>
<td>No</td>
<td>5 years</td>
</tr>
<tr>
<td>Khapra AP [29]</td>
<td>1998-2004</td>
<td>Retrospective single-center study</td>
<td>39 (n.a.)</td>
<td>No 47% at 10 years</td>
<td>Decrease with donor age</td>
<td>No</td>
<td>10 years</td>
</tr>
<tr>
<td>Ricchiuti A [30]</td>
<td>1998-2004</td>
<td>Retrospective single-center study</td>
<td>21 (n.a.)</td>
<td>No 81.5% at 5 years</td>
<td>No</td>
<td>No</td>
<td>5 years</td>
</tr>
<tr>
<td>Alvaro E [31]</td>
<td>2005-2011</td>
<td>Retrospective single-center study</td>
<td>13 (4)</td>
<td>No 81.5% at 5 years</td>
<td>No</td>
<td>No</td>
<td>6 years</td>
</tr>
<tr>
<td>Saab S [32]</td>
<td>1990-2000</td>
<td>Retrospective matched analysis</td>
<td>59 (n.a.)</td>
<td>No 64% at 5 years</td>
<td>No</td>
<td>No</td>
<td>5 years</td>
</tr>
<tr>
<td>Testa G [33]</td>
<td>1985-1995</td>
<td>Retrospective single-center study</td>
<td>22 (n.a.)</td>
<td>No 84% at 4 years</td>
<td>No</td>
<td>n.a.</td>
<td>4 years</td>
</tr>
<tr>
<td>Ghobrial RM [34]</td>
<td>1990-2000</td>
<td>Retrospective single-center study</td>
<td>59 (n.a.)</td>
<td>No 84% at 4 years</td>
<td>No</td>
<td>Increased fibrosis progression</td>
<td>10 years</td>
</tr>
<tr>
<td>Northup PG [35]</td>
<td>1994-1998</td>
<td>Register and comparative study</td>
<td>934 (n.a.)</td>
<td>No 67% at 5 years in HCVR+</td>
<td>n.a.</td>
<td>Increased fibrosis progression in HCVD+ older than 45</td>
<td>5 years</td>
</tr>
<tr>
<td>Lai JC [38]</td>
<td>2002-2007</td>
<td>Retrospective multicenter study</td>
<td>99 (n.a.)</td>
<td>No 73% at 3 years</td>
<td>No</td>
<td>Lower quality of the graft. Increased fibrosis progression in HCVD+ older than 45</td>
<td>5 years</td>
</tr>
</tbody>
</table>
No impact on survival

Case control Study
n=63

Controversial impact on recurrence

- Definition of recurrence?
- Lack of histological biopsy in most studies
- Impact of other criteria: age

HCV recurrence is curable

- SOF+RBV (1) 70%
- SOF+LDV (2) 95%
- SOF+DCV (3,4) 94%
- 3D (5) 95%
- SOF+SIM (6,7) 90%

### Pros and Cons

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
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<tr>
<td><strong>Limiting organ shortage and reducing mortality on waiting list</strong></td>
<td><strong>Concern only around 5% of donors</strong></td>
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</tbody>
</table>
| Effective screening methods (ELISA test and NAT) allow physicians to accurately match donors and recipients | When HCVR- received a graft from HCVD+/HCV RNA+, the risk of transmission is  
- constant transplanting liver  
- 48% transplanting kidney  
- 25% transplanting heart |
| Similar graft and patient survival compared to HCVD- except for HIV-HCV coinfected recipients | Lower quality of the graft even for HCVD+/HCV RNA-  
Possible increase in fibrosis progression (controversial) |
| Approval of multiple DAA, effective and safe after transplantation | Access to DAA is currently limited in many countries |
| An increasing number of HCV patients will be treated with DAA. As a result, an increasing number of HCV positive subjects in the general population are likely to be screened and cured. Therefore, anti-HCV positive donors are likely to become more frequently HCV-RNA negative. Their graft might be offered to HCVR- | Thanks to DAA, decompensated liver diseases related to HCV will be reduced as LT demands in this setting, reducing the number of HCVR+ |
Proposal to accept grafts from HCV infected donors

Thank you!

Centre hépato-Biliaire
A Coilly
B Roche
T Antonini
JC Duclos-Vallée
E De Martin
R Sobesky
F Saliba