UPDATE ON LIVER TRANSPLANTATION IN HIV 2013

JAMES O’BEIRNE
Royal Free Hospital
50 years of Liver Transplantation

- Surgical & Medical innovation
- Patient selection
Liver Disease in HIV-infected Patients

- Opportunistic diseases
- Hepatitis viruses
- Immune reconstitution
- Pre-existing diseases
- HCV treatment
- HIV treatment
- Fatty Liver Disease
- Alcohol abuse/IVDU

Causes of death in HIV


Includes primary liver cancer
HCV co-infection

• 1/3 rd of patients with HIV infection in Europe and the USA are co-infected with HCV
• 90% of deaths in HIV-positive patients with end-stage liver disease are attributed to HCV infection
  – HIV accelerates both HBV and HCV liver disease
  – HIV/HCV coinfection is associated with a reduced rate of spontaneous HCV RNA
  – More rapid rate of fibrosis progression
  – Following development of cirrhosis, the course of the liver disease is accelerated
  – median estimated survival time is only 13 months following the first decompensating event

HBV Co-infection

• 5-20% seroprevalence worldwide
• Variable effect upon HIV progression/recovery after cART
• Faster fibrosis progression
• Increased rates of Hepatocellular carcinoma

Hepatotoxicity is Seen With All Classes of ARV Drugs

ACTG retrospective analysis of 21 trials on 10,622 patients

- **NRTI:** 6.3%; 95% CI (5.8-6.8%)
- **NNRTI:** 8.2%; 95% CI (6.3-10.1%)
- **Protease Inhibitors:** 6.2%; 95% CI (5.2-7.2%)

- Liver related death rate was 0.3% (2.5% of all deaths)

• HIV increases the risk of ALF
• Efavirenz, Nevirapine, anti-TB etc....
• Usually severe in course
• 1.3% of Acute liver Failure in the USA (USALFSG)

HCC

- Increasing prevalence esp. in HCV
- May have a more aggressive phenotype
  - Younger age at presentation
  - Higher Median AFP

Liver Transplantation in HIV- historical aspects

- Pittsburgh 1990
- 25 patients (15 Liver tx)
- 11 infected prior to transplant
- 14 infected peri-operatively

In HIV+ patients who have no evidence of AIDS, transplantation can prolong meaningful life in the majority of patients but less reliably and less safely than in HIV- recipients. It is self-evident that the same statement could be made about virtually every other major medical or surgical therapy available today. Such therapies are not withheld from HIV+ patients because of a predictably lower efficiency or because of high cost.

Experience in the pre cART era

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Center</th>
<th>Diagnosis</th>
<th>Immunosuppression</th>
<th>Rejection/Treatment</th>
<th>AIDS-Defining Illness</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>Pittsburgh</td>
<td>N/A</td>
<td>C+P+OKT3</td>
<td>No</td>
<td>No</td>
<td>A:8m</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>Pittsburgh</td>
<td>HBV/HDV/NANB/H-A</td>
<td>C+P+OKT3</td>
<td>No</td>
<td>Yes: To (41 m); CMV (44 m)</td>
<td>D:44m</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>Pittsburgh</td>
<td>HBV/ALD/H-A</td>
<td>C+P</td>
<td>Yes:1 (OKT3+MoAb)</td>
<td>Yes: PCP (3 m)</td>
<td>D:4m</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>Pittsburgh</td>
<td>N/A</td>
<td>C+P+OKT3</td>
<td>No</td>
<td>No</td>
<td>D:9m</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>Pittsburgh</td>
<td>N/A</td>
<td>C+P+OKT3</td>
<td>No</td>
<td>Yes: immunoblastic sarcoma</td>
<td>D:8m</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>Pittsburgh</td>
<td>N/A</td>
<td>C+P</td>
<td>No</td>
<td>No</td>
<td>D:6m</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>Pittsburgh</td>
<td>N/A</td>
<td>C+P</td>
<td>No</td>
<td>No</td>
<td>A:68m</td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td>Pittsburgh</td>
<td>HBV/H-A</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>IOD</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>Mass. General</td>
<td>NANB/H-A</td>
<td>C+P+Az</td>
<td>Yes: 3 (steroids)</td>
<td>Yes: Cr (14 m); PCP (21 m)</td>
<td>D:27m</td>
</tr>
<tr>
<td>10</td>
<td>N/A</td>
<td>Deaconess</td>
<td>N/A</td>
<td>C+P</td>
<td>Yes: 3 (steroids+OKT3)</td>
<td>Yes: HSV, CMV</td>
<td>D:11m</td>
</tr>
<tr>
<td>11</td>
<td>N/A</td>
<td>Cambridge</td>
<td>ALD</td>
<td>C</td>
<td>Yes: 1 (steroids)</td>
<td>No</td>
<td>A:100m</td>
</tr>
<tr>
<td>12</td>
<td>35</td>
<td>Pittsburgh</td>
<td>HBV</td>
<td>T+C+P+PGE¹/PGE²</td>
<td>Yes: 3 (steroids)</td>
<td>Yes: CMV</td>
<td>D:70d</td>
</tr>
<tr>
<td>13</td>
<td>N/A</td>
<td>Omaha</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>D:2m</td>
</tr>
<tr>
<td>14</td>
<td>N/A</td>
<td>Omaha</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes: herpes zoster</td>
<td>A:9m</td>
</tr>
</tbody>
</table>
UK Experience

- 1\textsuperscript{st} case HIV+ve Haemophiliac transplanted at Kings College Hospital - 1996

Survival of HIV+ LT recipients in the post HAART era

• N=24 US/UK experience

Impact of HCV co-infection on LT outcome

Outcomes


Current UK guidelines for liver transplantation in HIV

**Box 1. UK guidelines for consideration of liver transplantation in HIV infection (in addition to the usual indications and contraindications).**

- Meets conventional criteria for listing for liver transplantation\(^1\) and:
  - CD4 counts of 200 cells/ml, or 100 cells/ml in the presence of portal hypertension
  - Absence of HIV viremia\(^2\)
  - Absence of AIDS-defining illness after immune reconstitution
  - Antiretroviral therapeutic options available if HIV disease reactivates

---

\(^1\)UK Model for End-Stage Liver Disease score >49, diuretic-resistant ascites or other variant syndrome, hepatic encephalopathy or hepatocellular carcinoma within accepted criteria.

\(^2\)Except in de novo presentation of HIV infection in cases of acute liver failure. Adapted with permission from [30].
UK Liver Transplant – number of transplants and number on waiting list

Figure 8.1  Deceased donor liver programme in the UK, 1 April 2001 - 31 March 2011
Number of donors, transplants and patients on the active transplant list at 31 March
Outcome of patients wait listed for Liver transplant in the UK

Figure 8.2  Post-registration outcome for 923 new elective liver only registrations made in the UK, 1 April 2007 - 31 March 2008

- 6 months:
  - Died/Removed: 4
  - Transplanted: 55
- 1 year:
  - Died/Removed: 6
  - Transplanted: 67
- 2 years:
  - Died/Removed: 3
  - Transplanted: 73

\(^1\) Removals due to condition deteriorating
Outcomes of HCV/HIV Liver Transplantation in recent cohorts – what can we learn?

- 27 HIV+ve patients undergoing LT (17 with HCV, 2012 n=26)
- 37% HCC
- Median Age 45 years
- MELD at LT = 15
- Median donor age 48 years

Outcomes of HCV/HIV Liver Transplantation in recent cohorts – what can we learn?

- Prospective multicentre cohort study
- 84 HCV/HIV co-infected LT patients 2002-2006 matched with non-HCV controls
- Majority Genotype 1
- MELD at listing 15 MELD at LT 16
- DRI 1.4
- Donor age (median) 52

Factors significant in multivariate analysis:
- MELD
- Genotype 1
- Transplant centre experience

Biopsy proven rejection
38% HCV/HIV  20% HCV

Outcomes of HCV/HIV Liver Transplantation in recent cohorts – what can we learn?

- $\text{Exp} \left([0.81966 \times \text{if genotype} = 1] + [0.05748 \times \text{MELD pre-OLT}] + [1.03540 \times \text{if center} < 1 \text{ OLT in HIV-infected patients/year}]\right)$

- Risk score cut-off of 1.07795 classified the 84 recipients as having a low risk (n = 60 patients, 69%) or a high risk of death (n = 24 patients 31%)

5 yr survival of Risk score < 1.077 = 69%

Outcomes of HCV/HIV Liver Transplantation in recent cohorts – what can we learn?

- Prospective study 89 patients 2003-2010
- 2 control groups
  - Matched
  - High risk group (>65 years old)

<table>
<thead>
<tr>
<th></th>
<th>HCV/HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49</td>
<td>54</td>
</tr>
<tr>
<td>BMI</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>MELD@LT</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>HCC %</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Genotype 1 %</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Donor Age</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>NHBD %</td>
<td>17</td>
<td>4</td>
</tr>
</tbody>
</table>

Outcomes of HCV/HIV Liver Transplantation in recent cohorts – what can we learn?

**Multivariate analysis of factors associated with mortality:**

- CLKT
- BMI < 21
- Anti-HCV positive donor
- Older donor age

In patients without these risk factors, survival no different to HCV patients > 65 yrs

**Biopsy proven rejection**

- 39% HCV/HIV
- 24% HCV

LT for HCV/HIV co-infection

Hope for the future?

- Photon-1 114 G1 (4% cirrhotic) 42 G3 (14% cirrhosis) HIV co-infection
- Sofosbuvir 400mg od + RBV 1000-1200mg
  - 12 weeks G3
  - 24 weeks G1
- SVR12
  - G1 76%
  - G3 67%
- Well tolerated
- No interactions with wide range of ARV
- No resistance mutants in viral breakthrough patients

Sofosbuvir and Ribavirin for the Treatment of Established Recurrent Hepatitis C Infection After Liver Transplantation: Preliminary Results of a Prospective, Multicenter Study

- Phase 2 Multicenter post LT
- 80% Genotype 1
- 88% treatment experienced
- 40% cirrhotic, 23% bridging fibrosis
- Sofosbuvir 400 mg od with increasing RBV as tolerated
- SVR 4 77%
- No immunosuppressant interactions
- 15% anaemia
- No death or graft loss

Pretransplant Sofosbuvir and Ribavirin to Prevent Recurrence of HCV Infection after Liver Transplantation

- 61 patients - multicentre
- Mostly HCC with G1 HCV 77% treatment experienced
- Median MELD of 8
- Sofosbuvir 400 mg od and RBV 1000-1200mg/day
- Upto 48 weeks treatment whilst awaiting LT
- 91% were HCV RNA –ve after 12 weeks of therapy
- 64% of patients HCV RNA –ve at time of LT were HCV-RNA negative 12 weeks post LT
- Only 1 patient rendered HCV RNA negative for > 30 days relapsed after LT
- Well tolerated

Lessons from the past that inform the future

Figure 2. Actuarial Risk of Recurrence of HBV, According to the Duration of Passive Prophylaxis with Anti-HBs Immune Globulin.

Figure 4. Actuarial Survival, According to the Duration of Passive Prophylaxis with Anti-HBs Immune Globulin.

LIVER TRANSPLANTATION IN EUROPEAN PATIENTS WITH THE HEPATITIS B SURFACE ANTIGEN

Didier Samuel, M.D., Rainer Muller, M.D., Graeme Alexander, M.D., Luigi Fassati, M.D., Béatrice Ducot, M.D., Jean-Pierre Benhamou, M.D., Henri Bismuth, M.D., and the Investigators of the European Concerted Action on Viral Hepatitis Study*
Barriers to LT

• Must meet the conventional listing criteria for liver transplantation in the UK

• Which means……
  – Stable methadone but no heroin, crack or cocaine/ other recreational drugs
  – Alcohol – risk of relapse, need for abstinence (life long) even where alcohol is a co-factor eg. in HCV

Conclusions

- Liver disease (including HCC) is prevalent and will continue to rise in HIV infected individuals
- Current results support the use of LT in selected individuals although results in HCV co-infection are currently sub-optimal
- DAAs offer hope for the future although data is limited
- Multidisciplinary approach mandatory