Viral Hepatitis And Liver Transplantation

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Dep. Gastroenterology
Hepatitis B
310% HBV infection in liver transplant recipients, in western countries.
Ege University Experience
Etiology (607 adult)
HBV Recurrence

No prophylaxis
HBIG or Lamivudin
HBIG+Lamivudin

0
10
20
30
40
50
60
70
80
90
100
%
Pre-Tx treatments

Post-Tx prophylaxis

Treatment of recurrent disease

Cirrhosis

Transplantation

Time
Goals of Antiviral Therapy
Pre Transplant

- To suppress the viral replication to undetectable HBV DNA levels.
  - To avoid post transplant recurrence (Without acquiring resistance)

- Control hepatic decompensation.

- Avoid transplant.
HBV DNA Level Pre-Transplant Predicts Risk of HBV Recurrence

In those patients with low HBV DNA levels recurrence rate was compatible with patients undergoing LTX with undetectable serum HBV DNA.

## Summary of Efficacy at Week 48

<table>
<thead>
<tr>
<th>% with HBV DNA &lt; 400 copies/mL</th>
<th>TDF (n=45)</th>
<th>TVD (n=45)</th>
<th>ETV (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD score Median change</td>
<td>71%</td>
<td>88%</td>
<td>73%</td>
</tr>
<tr>
<td>Absolute MELD Week 48 (median)</td>
<td>-2.0</td>
<td>-2.0</td>
<td>-2.0</td>
</tr>
<tr>
<td>CPT score Mean change</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>Absolute CPT Week 48 (median)</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Median ALT (U/L)</td>
<td>29</td>
<td>33</td>
<td>31</td>
</tr>
</tbody>
</table>

- An ITT noncompleterswitch = failure analysis was used
- Subjects who switched from blinded medication to open-label TVD were considered noncompleters in all 3 arms of the study
- Subjects who underwent orthotopic liver transplant (OLT) (6 total; 2 TDF, 4 FTC/TDF) are censored from the HBV DNA, serology, biochemical, MELD and CPT analyses

## Antiviral Therapy in Decompensated Cirrhosis

- **HBV DNA < 400 copies/mL %**
- **Tenfovor (n = 45)**
- **Tenfovor/Emtricitabine (n = 45)**
- **Entecavir (n = 22)**

<table>
<thead>
<tr>
<th>Wk</th>
<th>TDF</th>
<th>TVD</th>
<th>ETV</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>51</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>24</td>
<td>66</td>
<td>74</td>
<td>68</td>
</tr>
<tr>
<td>48</td>
<td>71</td>
<td>88</td>
<td>73</td>
</tr>
</tbody>
</table>

Schiff E, et al. AASLD 2009
Cirrhosis

Pre-Tx treatments

Post-Tx prophylaxis

Treatment of recurrent disease

Transplantation

Time
HBIG
+
Lamivudin
(or other nucs)
HBI G Regimens used in US LT Centers

183 pts from NIH HBV-OLT study.
- All high dose HBI G perioperatively.

<table>
<thead>
<tr>
<th>Maintenance</th>
<th>Recurrence (5 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) iv 10,000 IU/month</td>
<td>14%</td>
</tr>
<tr>
<td>B) iv 1,000-5,000 IU/month</td>
<td>3%</td>
</tr>
<tr>
<td>C) im 1,000-5,000 IU/month</td>
<td>10%</td>
</tr>
<tr>
<td>D) discontinuation of HBI G</td>
<td>10%</td>
</tr>
</tbody>
</table>

Degertekin et al AASLD 2008
Ege University Experience
Low dose HBIG+Lamivudin:

80 cases

5% recurrence

median 18 (3-73) months follow up
209 HBV

follow-up 18 (6-48) months

Cadaveric
100

HBV DNA (+):5
HDV :22

Living donor
109

HBV DNA (+):5
HDV :40

Reappearance of HBsAg after its initial disappearance post-OLT

HBV recurrence
5

11/209
5 %

Lam Plus Low-dose HBIG to Prevent Recurrent HBV Following LT

✓ 147 HBsAg-positive pts over 8 years.

✓ LAM at transplant listing

✓ HBIG IM 800 IU (7 days); 400-800 IU/ month

HBV recurrence 4% at 5 years.

Gane et al. Gastroenterology 2007;132(3):931-937
Can we stop HBIG
2 types of approaches;

- Active immunoprophylaxis or vaccination
- Discontinuation of HBIG and continuing prophylaxis with nucleoside analogues
HBV Vaccination: The first study from Spain reported encouraging results. However, these encouraging results were not confirmed in subsequent studies. To investigate the efficacy of HBV vaccination we conducted a study. We administered double course of double dose recombinant HBV vaccine, including pre-S antigens.
14 patients included into the study

Recombinant HBV vaccine (Genhevac HB; containing HBV pre-S1, pre-S2, and S gene)

Vaccination started one month after HBIg discontinuation, and lamivudine (100 mg/day) was given throughout the study.

The first cycle 0, 1-, 6-month schedule second cycle 0, 1-, 2-month schedule

Only 1 patient seroconverted

Adefovir For LAM-Resistant HBV Recurrence

With continued treatment, an increasing proportion of patients who remained in the study had undetectable serum HBV DNA levels.

Schiff et al. Liver Transplantation 2007
209 HBV

follow-up 18 (6-48) months

Cadaveric
100

HBV DNA (+):5
HDV :22

HBV recurrence
5

11/209 5%

Living donor
109

HBV DNA (+):5
HDV :40

HBV recurrence
6
STOP HBIG

Lamivudin+Adefovir

11 HBV recurrence

18 (6-48) months

HBV DNA (+) 1

HBV DNA (-) 7

3 Died HCC recurrence 2 HBV DNA (-)

11 HBV recurrence
Lamivudin+Adefovir

STOP HBIG

18 (6-48) months

HBV DNA (+)
1

Tenofovir

HBV DNA (-)
7

HBV DNA (-)
2

3 Died
HCC recurrence
2 HBV DNA (-)

Hepatitis C
HCV in Liver Transplant Recipients

Western Countries: %25-50

Türkiye: %10-20
HCV in Post-transplant Setting

- Acute Lobular Hepatitis: 75%
- FCH: 20%
- Non-Hepatitis: 5%
HCV in Post-transplant Setting

Chronic Hepatitis
- 25% 3-5 years
- 25% slower

Cirrhosis

20% 75%
HCV in Post-transplant Setting

Chronic hepatitis

25% 3-5 years
25% slower

Cirrhosis

Decompensation

survival
20%: 3 years

4 years
75%
# Graft Loss Due To Recurrence Of Primary Disease After Liver Transplantation

## Aetiology of Liver Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>90</th>
<th>1000</th>
<th>2000</th>
<th>3000</th>
<th>4000</th>
<th>5000</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV (181)</td>
<td>161</td>
<td>117</td>
<td>69</td>
<td>30</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>PSC (200)</td>
<td>166</td>
<td>137</td>
<td>84</td>
<td>68</td>
<td>40</td>
<td>19</td>
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<tr>
<td>AIH (103)</td>
<td>81</td>
<td>66</td>
<td>48</td>
<td>32</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>Cryptogenic/NAFLD (111)</td>
<td>93</td>
<td>70</td>
<td>50</td>
<td>38</td>
<td>24</td>
<td>10</td>
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<tr>
<td>Non acetaminophen related FHF (151)</td>
<td>111</td>
<td>94</td>
<td>66</td>
<td>41</td>
<td>28</td>
<td>13</td>
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<tr>
<td>PBC (531)</td>
<td>450</td>
<td>383</td>
<td>311</td>
<td>243</td>
<td>162</td>
<td>82</td>
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<tr>
<td>ALD (179)</td>
<td>135</td>
<td>116</td>
<td>82</td>
<td>51</td>
<td>24</td>
<td>5</td>
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<tr>
<td>Acetaminophen related FHF (55)</td>
<td>34</td>
<td>28</td>
<td>21</td>
<td>18</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

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Rowe IA et al. Transplant International 2008
Survival Of Patients After Liver Transplantation

Neuman UP et al. Transplantation 2007
ELTR

HBV

HCV

Survival %

Years

>=2000 : 3194
1995 to 2000 : 2705
1990 to 1995 : 1357
1985 to 1990 : 127
<1985 : 6

>=2000 : 1410
95 to 2000 : 1196
90 to 95 : 915
85 to 90 : 287
<1985 : 10

91% 86% 84%
83% 72% 67%
### Post-OLT treatment of Recurrent HCV

**PEGIFN + Ribavirin**

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Case (n)</th>
<th>EOT (%)</th>
<th>SVR (%)</th>
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</thead>
<tbody>
<tr>
<td>Rodriguez-Luna</td>
<td>Transplantation 2004</td>
<td>19</td>
<td>37</td>
<td>26</td>
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<tr>
<td>Ross</td>
<td>Clin Transplant 2004</td>
<td>16</td>
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<td>Dumortier</td>
<td>J. Hepatology 2004</td>
<td>20</td>
<td>55</td>
<td>45</td>
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<td>Castells</td>
<td>J. Hepatology 2005</td>
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<td>58</td>
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<td>Neumann</td>
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<td>24</td>
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<td>Mukherjee</td>
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<td>39</td>
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<tr>
<td>Berenguer (a/b)</td>
<td>Liver Transplant 2006</td>
<td>67</td>
<td>46</td>
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<td>Fernandez</td>
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<td>Chadalavada</td>
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<td>Oton</td>
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<td>Zimmermann</td>
<td>Transplant International 2007</td>
<td>26</td>
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</table>

Although, in post-transplant patients with recurrent chronic hepatitis C virus infection, end of treatment virologic responses are compatible to those non-transplant patients, sustained virologic response rate is lower in the post-transplant setting.
Slow or late responders to PEG-IFN and ribavirin may benefit from an extended treatment course.
Extending Therapy in Slow Responders

End of treatment virological response was comparable in 48-72w groups, SVR was significantly higher among patients treated for 72 weeks

Ferenci P. et al. AASLD 2006. Abstract 390
**Ege University Experience**

<table>
<thead>
<tr>
<th>Week</th>
<th>HCV RNA</th>
<th>HCV RNA</th>
<th>HCV RNA</th>
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<td>120</td>
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<td>144</td>
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</tbody>
</table>

**IFN alpha 2b 3MU TIW**

+ **Ribavirin (800-1000 mg / day)**

**PEG IFN 1,5 microgram / kg**

+ **Ribavirin (800-1000 mg / day)**

**HCV RNA (+)**

Stop therapy

Proper data on early or late virologic responders were not available while we were planning the study. We proposed that the interferon-induced immune response against hepatitis viruses might be slower in immunosuppressed patients and prolongation of treatment may increase the response rate. Although we had no reference regarding total duration, we chose three years of treatment.
Since all six patients who could clear the virus after one year of treatment achieved sustained virologic response after three years of therapy, that duration may be enough or more than enough. Considering that none of the responders experienced a relapse, more than one year of therapy would be advisable for those who could clear the virus within one year.

Karasu Z et al. APASL 2007
Transplant Proceedings 2009
21 patients
PEG-IFN + Ribavirin

3 HCV RNA (+)
49 (24-77) month therapy

4 HCV RNA (+)

14 HCV RNA (-)
66 (20-94) month therapy

13 HCV RNA (-)

Kornberg A. Journal of Gastroenterology and Hepatology 2007
Thank You

$\text{Thank You}$