Liver transplantation for HCV and HBV in The Czech Republic

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Disclosures

• Speaking fees: Abbvie, Gilead, MSD, Novartis
Liver transplantation

• June 1983

  Consensus Conference on Liver transplantation in Bethesda, USA.

• Liver transplantation was declared as valid therapy for end stage liver disease.

Conclusion

“After extensive review and consideration of all available data, this panel concludes that liver transplantation is a therapeutic modality for end-stage liver disease that deserves broader application. However, in order for liver transplantation to gain its full therapeutic potential, the indications for and results of the procedure must be the object of comprehensive, coordinated, and ongoing evaluation in the years ahead. This can best be achieved by expansion of this technology to a limited number of centers where performance of liver transplantation can be carried out under optimal conditions. “
Two liver transplant centres in CR
1st liver transplantation in Czechoslovakia

- Brno, 2 February 1983, professor Kořístek

https://www.cktch.cz/od-prvni-transplantace-jater-uplynulo-35-let/t2242
Liver transplantation in IKEM, Prague, since 1995

https://www.facebook.com/ikemcz

![Liver transplantation chart]

- **No. Tx** (Transplantation)
- **No. reTx** (Re-transplantation)

Yearly distribution from 1995 to 2017:
- 1995: 13
- 1996: 25
- 1997: 30
- 1998: 39
- 1999: 45
- 2000: 39
- 2001: 38
- 2002: 39
- 2003: 34
- 2004: 56
- 2005: 57
- 2006: 66
- 2007: 74
- 2008: 63
- 2009: 69
- 2010: 70
- 2011: 60
- 2012: 80
- 2013: 81
- 2014: 109
- 2015: 121
- 2016: 114
- 2017: 137

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>1 year</th>
<th>2 years</th>
<th>5 years</th>
<th>7 years</th>
<th>10 years</th>
<th>15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grafts</td>
<td>92.38 %</td>
<td>86.65 %</td>
<td>83.97 %</td>
<td>78.78 %</td>
<td>74.94 %</td>
<td>69.27 %</td>
<td>59.34 %</td>
</tr>
<tr>
<td>Patients</td>
<td>96.12 %</td>
<td>91.25 %</td>
<td>88.9 %</td>
<td>84.22 %</td>
<td>80.46 %</td>
<td>75.28 %</td>
<td>65.73 %</td>
</tr>
</tbody>
</table>
Specific situation in the Czech Republic

- **HCV infection**
  - Very low prevalence
    - 0.2% in 2001
    - 0.9% in 2015
  - Genotype 1b used to be the most prevalent (until 2008)

- **HBV infection**
  - Also a low prevalence
  - 0.56% HBsAg +, 5% anti-HBc total + in 2001
  - Less than 100 acute infections reported annually in the last 5 years
  - Since 2001: general vaccination of infants


- Alcoholic 21.0%
- HCV 10.0%
- HCC 13.3%
- PSC 10.3%
- PBC 5.9%
- Autoimmune 4.2%
- Kryptogenic + NASH 6.2%
- Wilson chronic 1.1%
- Polycystic liver 3.8%
- Liver tumors (other) 2.4%
- Metabolic 2.0%
- Biliary atresia 2.8%
- HBV 2.8%
- Others 8.4%
- ALF 8.9%
- 17%
- 0%
- HIV +
- HCC 13.3%
- 17%
Liver transplantation for HCV

• HCV recurrence in the liver graft was universal and influenced negatively survival of LTx recipients

• Peginterferon-α based treatments regimens efficacy was poor with a high rate of serious adverse events
Liver transplant recipients survival, IKEM, 1995-2013, HCV vs. other diagnoses

Šperl et al, 2013.
Interferon-based treatment related adverse events

- Anaemia
- Flu-like syndrome, life-threatening infections
- Rash
Anti-HCV therapy in IKEM in the IFN era: 1995-2014

44%
Survival of HCV patients according to SVR (IKEM, 1995-2013)

Šperl et al., 2013.
DAA in treatment of post-LTx recurrence

• In the DAA era, only a minority of patients have a contraindication to therapy
• DAA use increases treatment efficacy
• The rate of treatment-related adverse events is low
HCV patients’ characteristics

• 7/1995 - 2/2018
• 199 patients (12.7% of 1573 total LTx recipients)
  • 128 males, 71 females
  • average age 55.1 ± 8.2 years
  • 80 had HCC or iHCC (40%)
  • 97.5% of patients were infected with genotype 1b
Genotype distribution in LTx patients in comparison with "general population" infected individuals

<table>
<thead>
<tr>
<th>HCV</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>∑ = 199</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>194 (97,5%)</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>3 (1.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Therapeutical options used

• 1995-2002: conventional interferon α ± ribavirin
• 2002-2012: pegylated interferon α ± ribavirin
• 2012-2014: pegylated interferon α ± ribavirin ± first generation protease inhibitors

• from May 2014: „DAA era“
• different combinations according to local DAA availability and their reimbursement
Patients’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>IFN era</th>
<th>DAA era</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Patients’ age (mean, years)</td>
<td>54</td>
<td>60</td>
<td>&lt;0.001</td>
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<tr>
<td>HCC occurrence (%)</td>
<td>33%</td>
<td>64%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to first therapy, (median, days)</td>
<td>317</td>
<td>112</td>
<td>&lt;0.001</td>
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DAA treatment regimens after LTx

<table>
<thead>
<tr>
<th>DAA regimen</th>
<th>No. patients</th>
</tr>
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<tbody>
<tr>
<td>SOF+RBV</td>
<td>2</td>
</tr>
<tr>
<td>SOF+DCV</td>
<td>11</td>
</tr>
<tr>
<td>SOF+SIM</td>
<td>12</td>
</tr>
<tr>
<td>SOF+LDV±RBV</td>
<td>27</td>
</tr>
<tr>
<td>PAR/r+OMB+DSV±RBV</td>
<td>16</td>
</tr>
<tr>
<td>GRA/ELB</td>
<td>5</td>
</tr>
</tbody>
</table>
Results

• In total, **73 HCV patients** were treated from May 2014

• **Salvage therapy**
  • 42 patients
  • Those with severe graft fibrosis or cirrhosis were prioritized
  • Failure of previous therapies with P/R
  • Contraindications to P/R therapy
  • Median treatment initiation 90 months (7.5 years) after LTx

• **Immediate therapy**
  • 31 patients started treatment immediately after HCV recurrence was proven in the liver graft by biopsy
  • Mean treatment initiation was 112 days (3.7 months) after LTx
## Patients’ characteristics

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Liver transplantation for HCV (N=199)

IFN era N=152
- Treatment failure
  - Contraindication
    - Death N=110
  - SVR N=42 44%
- SVR pre-LTx N=9

DAA era N=47
- Salvage therapy N=42
  - SVR 41/42 98%
- Immediate therapy N=31
  - SVR 28/31 90%

The difference in SVR was not statistically significant between groups (P=0.1)
Anti-HCV therapy in IKEM: 1995-2018

SVR achievement (%)

IFN: 44%
DAA: 93.7%
SVR according to DAA regimen after LTx

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<th>DAA regimen</th>
<th>SVR %</th>
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<tbody>
<tr>
<td>SOF+RBV</td>
<td>50</td>
</tr>
<tr>
<td>SOF+DCV</td>
<td>100</td>
</tr>
<tr>
<td>SOF+SIM</td>
<td>92.7</td>
</tr>
<tr>
<td>SOF+LDV</td>
<td>93</td>
</tr>
<tr>
<td>PAR+OMB+DSV</td>
<td>100</td>
</tr>
<tr>
<td>GRA+ELB</td>
<td>100</td>
</tr>
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Survival of HCV LTx patients in IKEM: 1995-2014 vs. 2014-2018

- None of the patients died of fibrosing cholestatic hepatitis
- None of the patients underwent re-transplantation

p = 0.0062
HBV patients’ characteristics

- 6/1999 - 7/2018
- 69 patients (4.1% of 1667 total LTx recipients)
  - 49 males, 20 females
  - average age 53.7 ± 9.7 years
  - 26 had HCC or iHCC (37.7%)
Indication for liver transplantation in HBV

- Cirrhosis B: 34
- HCC: 26
- Fulminant liver failure: 9
Anti-HBV prophylaxis

• HBIG
  • High dose protocol
  • Long-term administration according to anti-HBs levels
• + NUC analogue

<table>
<thead>
<tr>
<th>NUC</th>
<th>Since</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBIG+LAM</td>
<td>1999</td>
<td>31</td>
</tr>
<tr>
<td>HBIG+ADV</td>
<td>2005</td>
<td>5</td>
</tr>
<tr>
<td>HBIG+TDF</td>
<td>2008</td>
<td>16</td>
</tr>
<tr>
<td>HBIG+ETV</td>
<td>2010</td>
<td>16</td>
</tr>
<tr>
<td>HBIG+ETV+TDF</td>
<td>2010</td>
<td>1</td>
</tr>
</tbody>
</table>
Recurrence of HBV in the liver graft

- Defined as reappearance of HBsAg
- 7 patients (10.1%)

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Recurrence (No. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBIG+LAM</td>
<td>4</td>
</tr>
<tr>
<td>HBIG+ADV</td>
<td>1</td>
</tr>
<tr>
<td>HBIG+ETV</td>
<td>2</td>
</tr>
</tbody>
</table>

No HBV DNA detected at the time of recurrence, all 3 had HCC

- The type of administered prophylaxis was not a risk factor for HBV recurrence (p=0.43)
- 2 patients eliminated HBsAg on ADV which was administered as salvage therapy
Survival of HBV LTx patients in IKEM: 1999-2018

None of the patients died owing to HBV recurrence or had retransplantation due to liver graft cirrhosis.
Conclusions

• With the use of highly effective antivirals, patients with viral hepatitis B and C have an excellent survival after liver transplantation.

• We achieved HCV microelimination in the group of liver transplant patients.

• In the future, the incidence of HBV and HCV-related decompensated cirrhosis will continue to decrease, but the patients with HCC will continue to represent potential candidates for transplantation.
Thank You for Your attention.