LIVER TRANSPLANTATION FOR OVERLAP SYNDROMES OF AUTOIMMUNE LIVER DISEASES

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Dr. Montano-Loza, supervisor
No conflict of interest
Overview

- Objectives
- Introduction
- Methods
- Results
- Conclusions
Liver Transplantation For Overlap Syndromes Of Autoimmune Liver Diseases

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Liver Transplantation For Overlap Syndromes Of Autoimmune Liver Diseases

- Recognize the clinical course of patients with overlap syndromes
- Appreciate post-transplant outcomes in patients with overlap syndromes
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Overlap syndromes are defined as variant forms of autoimmune hepatitis (AIH) with characteristics encompassing either primary biliary cirrhosis (PBC), or primary sclerosing cholangitis (PSC)
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- AIH is a chronic inflammatory liver disease
- Aminotransferases can range from mildly elevated to > 1000 U/L. Presence of autoantibodies (ANA, anti-actin), elevated levels of IgG and IgM
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- Lobular inflammation
- Interface hepatitis
- Portal triad
- Biliary ducts
- Portal arteriole
- Portal vein
- Interlobular biliary duct
- “Limitant plate”
PBC is a slowly progressing autoimmune disease that mainly affects women.

- Fatigue and pruritus are most common symptoms.
Most patients have antimitochondrial antibodies, and elevated IgM levels. Serum bilirubin is elevated in progressive disease.

Liver biopsy is not necessary to make the diagnosis, but it can help determine the stage of disease.
PBC: “florid duct lesion”
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- PSC is a chronic condition with progressive bile duct inflammation and destruction

- It is more common in males, most common symptoms include fatigue and pruritus
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Liver Transplantation For Overlap Syndromes Of Autoimmune Liver Diseases

- Approximately 25% of liver transplants are performed for autoimmune liver diseases
- Prevalence of recurrent disease increases with time following transplant
The following recurrence rates have been reported 5 years following transplant:

- AIH 17-42%
- PBC 12-13%
- PSC 12-60%

references 4-8
Overlap syndromes are uncommon, hence studies documenting outcomes in this group post-transplant are lacking.
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231 patients (22%) with end-stage autoimmune liver disease who received liver transplant from 1989-2010 were evaluated.

Data was recovered from the Organ Transplant Tracking Record (OTTR) database.
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- Recurrent AIH was defined as presence of lymphoplasmacytic infiltrates in liver tissue, elevated serum immunoglobulins, presence of autoantibodies, or sustained elevations of aminotransferases.

- Recurrent PBC was defined as compatible liver histology.
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- Recurrent PSC was defined by characteristic findings seen on cholangiography.

- Recurrent Overlap syndrome was defined by development of features of one or two autoimmune liver diseases in patients who received liver transplant for end-stage Overlap syndromes.
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- Graft loss was defined as death or re-transplantation

- Survival was defined from the date of liver transplant to date of last follow up or death
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Liver Transplantation For Overlap Syndromes Of Autoimmune Liver Diseases

<table>
<thead>
<tr>
<th>Features at Liver Transplantation</th>
<th>Overlap Syndrome (n = 12)</th>
<th>AIH (n = 32)</th>
<th>PBC (n = 103)</th>
<th>PSC (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43±5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46±3</td>
<td>53±1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>45±1</td>
</tr>
<tr>
<td>Female: male</td>
<td>9: 3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21: 11</td>
<td>88: 15</td>
<td>18: 66&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>7 (58)</td>
<td>18 (56)</td>
<td>86 (84)</td>
<td>74 (89)</td>
</tr>
<tr>
<td>Canadian First Nations</td>
<td>0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3 (9.5)</td>
<td>13 (13)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (8)</td>
<td>0</td>
<td>2 (1.5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other*</td>
<td>4 (34)</td>
<td>11 (34.5)</td>
<td>2 (1.5)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Time Diagnosis and LT (mo)</td>
<td>35±11&lt;sup&gt;d,e,f&lt;/sup&gt;</td>
<td>136±22&lt;sup&gt;d&lt;/sup&gt;</td>
<td>89±10&lt;sup&gt;e&lt;/sup&gt;</td>
<td>93±14&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bilirubin (nl,&lt;20 μmol/L)</td>
<td>276±111</td>
<td>135±38</td>
<td>276±30</td>
<td>234±29</td>
</tr>
<tr>
<td>INR</td>
<td>1.5±0.1</td>
<td>1.5±0.1</td>
<td>2.4±0.5</td>
<td>1.9±0.3</td>
</tr>
<tr>
<td>MELD Score</td>
<td>19±4.5</td>
<td>17±1.9</td>
<td>19±1.2</td>
<td>19±1.2</td>
</tr>
</tbody>
</table>

Significantly different from each other at the level of <sup>a</sup>P=0.005; <sup>b</sup>P<0.001; <sup>c</sup>P<0.001; <sup>d</sup>P=0.004; <sup>e</sup>P=0.01; and <sup>f</sup>P=0.01.

*Includes blacks, and unknown. Numbers in parentheses are percentages.
# Liver Transplantation For Overlap Syndromes Of Autoimmune Liver Diseases

<table>
<thead>
<tr>
<th>Features After Liver Transplantation</th>
<th>Overlap Syndrome ($n = 12$)</th>
<th>AIH ($n = 32$)</th>
<th>PBC ($n = 103$)</th>
<th>PSC ($n = 83$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living-related Transplant</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Immunosuppression:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>5 (42)</td>
<td>13 (41)</td>
<td>32 (31)</td>
<td>27 (32)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>8 (67)</td>
<td>22 (69)</td>
<td>62 (60)</td>
<td>62 (74)</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>4 (33)</td>
<td>8 (25)</td>
<td>46 (48)</td>
<td>23 (27)</td>
</tr>
<tr>
<td>Mycophenolate Mofetil</td>
<td>8 (67)</td>
<td>20 (63)</td>
<td>44 (43)</td>
<td>48 (57)</td>
</tr>
<tr>
<td>Steroids</td>
<td>9 (75)</td>
<td>28 (88)</td>
<td>73 (71)</td>
<td>49 (58)</td>
</tr>
<tr>
<td>Rejection Episodes</td>
<td>4 (33)</td>
<td>10 (31)</td>
<td>57 (55)</td>
<td>32 (38)</td>
</tr>
</tbody>
</table>

Significantly different from each other at the level of $^aP=0.05$, $^bP=0.008$, and $^cP=0.03$. Numbers in parentheses are percentages.
# Liver Transplantation For Overlap Syndromes Of Autoimmune Liver Diseases

<table>
<thead>
<tr>
<th></th>
<th>AIH-PBC (n=7)</th>
<th>AIH-PSC (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Disease(s)</td>
<td>PBC (n=2)</td>
<td>PSC (n=1)</td>
</tr>
<tr>
<td></td>
<td>AIH (n=1)</td>
<td>AIH (n=1)</td>
</tr>
<tr>
<td></td>
<td>AIH-PBC (n=1)</td>
<td>AIH-PSC (n=1)</td>
</tr>
</tbody>
</table>
## Liver Transplantation For Overlap Syndromes Of Autoimmune Liver Diseases

<table>
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<tr>
<th>Outcome after Liver Transplantation</th>
<th>Overlap Syndrome (n = 12)</th>
<th>AIH (n = 32)</th>
<th>PBC (n = 103)</th>
<th>PSC (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence During Follow-Up</td>
<td>5 (42)</td>
<td>9 (28)</td>
<td>26 (25)</td>
<td>24 (29)</td>
</tr>
<tr>
<td>Recurrence at 1-year (%)*</td>
<td>9&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>11</td>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Recurrence at 5-years (%)*</td>
<td>46&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>16</td>
<td>16&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Recurrence at 10-years (%)*</td>
<td>64&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>33</td>
<td>26&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Significantly different from each other at the level of <sup>a</sup>P=0.003; and <sup>b</sup>P=0.04.

* Calculated using the Kaplan-Meier method, and compared using the Log-Rank. Numbers in parentheses are percentages.
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<table>
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<tr>
<th>Pt followed (no.)</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>12 8 4 3 1 1 1</td>
</tr>
<tr>
<td>AIH</td>
<td>32 23 18 11 10 8</td>
</tr>
<tr>
<td>PBC</td>
<td>103 81 69 62 43 31</td>
</tr>
<tr>
<td>PSC</td>
<td>84 68 51 42 26 20</td>
</tr>
</tbody>
</table>

Recurrence (%)

OS vs. OS, Log-Rank, P=0.1
AIH vs. OS, Log-Rank, P=0.003
PBC vs. OS, Log-Rank, P=0.04
Liver Transplantation For Overlap Syndromes Of Autoimmune Liver Diseases

Survival (%) vs. OS, Log-Rank, P=0.4

OS vs. OS, Log-Rank, P=0.5

OS vs. OS, Log-Rank, P=0.8

Pt followed (no.)
OS 12 12 7 6 3 2 1
AIH 32 25 19 12 10 8 6
PBC 103 85 77 71 60 53 40
PSC 84 73 57 49 43 35 27

Follow-up (mo)
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Overlap syndromes are an uncommon indication for liver transplantation.

Recurrence in these patients may involve either single autoimmune liver disease or Overlap syndrome.
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- The higher rate of recurrence post transplant and short duration from diagnosis to transplant in Overlap syndrome, may be a reflection of more aggressive disease.

- Despite this neither graft survival nor patient survival was affected.
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- Acknowledgement
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References:


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- **References:**


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