Elevation in Liver Transamininase (ALT-flares) in Transplant (TX) Recipients: Risk Factors and Consequences

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DISCLOSURES

NONE
The **Management of post Transplant infections in Collaborating Hospitals** (MATCH) program was established in 2011 at Rigshospitalet, Copenhagen, Denmark.

MATCH aims to prevent infectious disease complications in the course of solid organ- (SOT) and hematopoietic stem-cell -transplantation (HSCT).

One section of the MATCH program focuses on better understanding the clinical implications of liver injury in transplant recipients.
BACKGROUND

- Destruction of hepatocytes $\rightarrow$ leakage of intracellular enzymes into the blood, incl alanine aminotransferase (ALT) $\rightarrow$ increases blood level of ALT $\rightarrow$ ALT-flare

- Caused by viral infections$^{1,2}$, other systemic infections$^3$, drug-induced-liver-injury (DILI)$^4$-$^6$ and immunological reactions

- Risk factors, prognostic information, and possible causes of ALT-flares were poorly described in the literature for TX-recipients

HYPOTHESIS

ALT-flares in transplant recipients occur frequently and because of multiple reasons, but regardless of cause of flare and TX-type have negative impact on survival

METHODS

Retrospective, grand-scale observational study

Patient cohort
• Solid Organ- (SOT) and Hematopoietic Stem-Cell Transplantation (HSCT) recipients
• All consecutively transplanted between September 2009 and June 2013 at our hospital
• Followed up from TX as routine care until either death, loss-to-follow-up (+ 60 days) or 22\textsuperscript{nd} October 2013

ALT-flare
• Start of flare: ALT-value twice the minimum value and above 70 IU/ml
• Severity of flare: Maximum ALT value, above the upper limit of normal (ULN)
METHODS

Data collection

• MATCH database collate demographics, clinical variables, medicines used and results of biochemical/microbiological analysis (e.g. ALT measurements) determined as part of routine care

• For this analyses - patient chart reviewed of details around each ALT-flare (symptoms, diagnosis) and events preceding all observed deaths

Statistical analysis

• Poisson regression for incidence rate ratio (IRR) of flare and death
RESULTS – characteristics of cohort

- **1002 transplant recipients**
  - SOT: 665
  - HSCT: 337

- **Follow-up**
  - 1937 person-years of FU
  - Median: 21.6 months (IQR: 10.8-34.8)
  - 153 died

- **ALT-flares post-tx**
  - Total #: 1220
  - Number of patients with
    - No flare: 500 (49.9%)
    - 1 flare: 230 (23.0%)
    - 2 flares: 113 (11.3%)
    - 3 or more flares: 159 (15.9%)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>No ALT flare</th>
<th>1+ ALT flare</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>1002</td>
<td>500</td>
<td>502 (50.1%)</td>
</tr>
<tr>
<td>Heart</td>
<td>47</td>
<td>27</td>
<td>20 (42.6%)</td>
</tr>
<tr>
<td>Liver</td>
<td>170</td>
<td>50</td>
<td>120 (70.6%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>328</td>
<td>200</td>
<td>128 (39.0%)</td>
</tr>
<tr>
<td>Lung</td>
<td>120</td>
<td>34</td>
<td>86 (71.7%)</td>
</tr>
<tr>
<td>HSCT</td>
<td>337</td>
<td>189</td>
<td>148 (44.0%)</td>
</tr>
</tbody>
</table>
Time from transplantation to 1st flare

P < 0.0001
Time from 1\textsuperscript{st} to 2\textsuperscript{nd} flare

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Proportion with 2\textsuperscript{nd} ALT flare over weeks after 1\textsuperscript{st} flare.}
\end{figure}

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
N & Heart & Liver & Kidney & Lung & HSCT \\
\hline
Heart & 20 14 & 13 & 12 & 9 \\
Liver & 117 82 & 60 & 46 & 25 \\
Kidney & 126 122 & 116 & 105 & 87 \\
Lung & 86 61 & 46 & 41 & 30 \\
HSCT & 144 100 & 62 & 40 & 25 \\
\hline
\end{tabular}
\end{table}

\textbf{P < 0.0001}
Factors associated with flare development / adjusted model

Factors adjusted for in the model: Age, Gender, Year TX, Weeks since TX, TX-type, Re-TX, Reason TX*

* 1=reduced perfusion, 2=acute insufficiency/organ failure, 3=chronic organ failure, 4=reduced function due to chronic impact, 5=autoimmune/hereditary disease, 6=malignancy, 7=unknown/unreported.
Risk of death associated with number and severity of ALT-flares

*Factors adjusted for in the model: Age, Gender, Year TX, Weeks since TX, TX-type, Re-TX, Reason TX, number of flares and ULN+ of flare (pr. 5 IU/ml)
Factors adjusted for in the model: Age, Gender, Year TX, Weeks since TX, TX-type, Re-TX, Reason TX* and number of flares

* 1=reduced perfusion, 2=acute insufficiency/organ failure, 3=chronic organ failure, 4=reduced function due to chronic impact, 5=autoimmune/hereditary disease, 6=malignancy, 7=unknown/unreported.
Type of flare and association w. death

*HF=Heart Failure, OF=Organ Failure

**Factors adjusted for in the model: Age, Gender, Year TX, Weeks since TX, TX-type, Re-TX, Reason TX* and number of flares

Other: Biliary (7 deaths), TX-related (6 deaths), cancer/OF (4 deaths) and other (6 deaths)
Limitations/strength

LIMITATIONS
- Unable to access all specific types of medicines the recipients received.
- Observational studies are unable to determine causal links → rational basis for more focused studies

STRENGTHS
- The large patient cohort
- The diverse characteristics of the cohort, including all different transplantation types → universally applicable
- Great and detailed amounts of data on diverse clinical variables
CONCLUSION

• ALT-flares occurs frequently during the course of transplantation

• Several ALT-flares, in particular if severe, are major prognostic factors of mortality, irrespective of type of transplantation

• Future studies should examine potential biological mechanisms explaining the association
QUESTIONS?
THANK YOU

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