Dr Sion Williams
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Quantification of hepatic FOXP3+ T-lymphocytes in HIV-hepatitis C co-infection - a mechanism for poor outcomes?

SK Williams, E Donaldson, T Van der Kleij, L Dixon, M Fisher, J Tibble, Y Gilleece, P Klenerman, AH Banham, M Howard, DP Webster
Liver disease in HIV
Mortality

Joshi et al. Increasing burden of liver disease in patients with HIV infection. Lancet 2011; 377: 1198-1209
History of HCV infection

Transmission¹

HIV co-infection

Chronic carriage¹

Fibrosis²

End stage liver disease²

HCV-infected liver

Effector T-lymphocytes

CD8+

Damage

Inhibition

FOXP3+ CD4+

Regulatory T-lymphocytes
FOXP3 is a transcription factor in Treg
- Treg marker
- Protective against cytotoxic T-cells
- Significant role in HCV
- Inversely proportional to fibrosis in HCV
- No studies in co-infected patients

Hypothesis

Fewer hepatic FOXP3+ Treg cells in subjects with HIV/HCV co-infection compared with HCV mono-infection may explain the poorer clinical outcome.
FOXP3 cells in HIV-HCV co-infection study

- Retrospective, cross-sectional
- Archived liver biopsies from Sussex patients
- 35 participants
  - HCV mono-infected (11)
  - HIV/HCV co-infected (12)*†
  - HIV mono-infected (12)*
- Male, non-African, no HepB
- Matched
  - Age (+/- 7 yrs)
  - Fibrosis (ISHAK)

<table>
<thead>
<tr>
<th></th>
<th>Mean (range)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>47 (34-61)</td>
</tr>
<tr>
<td>ISHAK score (/6)</td>
<td>2 (0-6)</td>
</tr>
<tr>
<td>Blood CD4‡ (x10⁶/L)</td>
<td>570 (230-950)</td>
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*HIV-1 infected
†11 of 12 on HAART
• Quantified FOXP3+, CD8+, CD4+ and CD20+ cells
• Indirect immunohistostaining and light microscopy
HIV/HCV co-infected patients have significantly fewer hepatic FOXP3+ cells and more CD8+ cells than HCV mono-infected patients.
HIV/HCV co-infected patients have a significantly lower hepatic FOXP3:CD8 ratio than HCV mono-infected patients.

HIV/HCV co-infected patients have a significantly fewer hepatic CD20+ cells than HCV mono-infected patients.
Reduced regulatory activity dependent on hepatic CD4 count

Dependent variable (OR) of HCV mono-infected : HIV-HCV co-infected

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>P value</th>
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<tbody>
<tr>
<td>FOXP3</td>
<td>1.1</td>
<td>0.05</td>
</tr>
<tr>
<td>CD4 (liver)</td>
<td>1.1</td>
<td>0.02</td>
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<tr>
<td>FOXP3</td>
<td>1.01</td>
<td>0.8</td>
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Discussion

• Fewer FOXP3+ cells in livers of co-infected patients suggests lower regulatory activity
• More CD8+ cells in co-infected patients suggests higher cytotoxic activity
• Fewer CD20+ cells suggests weakened humoral immunity
• This picture may explain why HCV/HIV co-infected patients have worse outcomes
• Rationale for starting HAART earlier in co-infected patients?
Thank you for listening.

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