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Polymorphisms at genes involved in the purine metabolic pathway influence the risk of non-cirrhotic portal hypertension (NCPH) in HIV-infected patients

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18th Annual Conference of the British HIV Association
18-20 April 2012, Birmingham, UK
Liver disease in HAART era is one of the leading cause of mortality and morbidity

Cause of liver abnormalities remain unknown for some groups of HIV positive patients

NCPH is one of the rare but potentially life threatening complication of HAART

Soriano et al, 2008; Maida et al, 2006; Weber et al, 2006
Aetiology of variceal bleeding in 48 HIV patients over 10 years

Scourfield et al. BHIVA 2011 Abstract O6
Background 2

• NCPH described as the features of portal hypertension in the absence of cirrhosis on liver biopsy

• Prior exposure to ddI (+cumulative use) recognized as the most important predisposing factor

• The prevalence of NCPH is very low despite the large number of patients exposed to ddI

Vispo et al 2011; Maida et al, 2005; Mallet et al, 2007; Schiano et al, 2007
## ddl exposure and NCPH

<table>
<thead>
<tr>
<th></th>
<th>Median months exposure (IQR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NCPH (n=16)</td>
<td>Cohort (n=6,360)</td>
</tr>
<tr>
<td><strong>AZT</strong></td>
<td>41 (10 to 60.5)</td>
<td>20.5 (6.3 to 54.8)</td>
</tr>
<tr>
<td><strong>D4T</strong></td>
<td>14.5 (0.0 to 30.5)</td>
<td>28.6 (10.8 to 56.6)</td>
</tr>
<tr>
<td><strong>DDI</strong></td>
<td>59.5 (44.5 to 82.0)</td>
<td>21.1 (7.18 to 54.33)</td>
</tr>
<tr>
<td><strong>TDF</strong></td>
<td>35.5 (4.5 to 50.5)</td>
<td>27.4 (8.3 to 51.7)</td>
</tr>
<tr>
<td><strong>ABC</strong></td>
<td>13.5 (0 to 59.0)</td>
<td>28.5 (12.1 to 67.0)</td>
</tr>
<tr>
<td><strong>3TC or FTC</strong></td>
<td>22.5 (9.0 to 57)</td>
<td>36.5 (12.4 to 76.4)</td>
</tr>
<tr>
<td><strong>Any PI</strong></td>
<td>22 (7.5 to 47.5)</td>
<td>30.7 (11.2 to 62.7)</td>
</tr>
<tr>
<td><strong>Any NNRTI</strong></td>
<td>65.5 (33.5 to 87.5)</td>
<td>27.5 (9.0 to 66.8)</td>
</tr>
</tbody>
</table>

Scourfield et al, 2011
Proposed mechanisms

• Coagulation and thrombophilia
• Bacterial translocation
• Mitochondrial toxicity
• Chronic HIV related inflammation
• Genetic polymorphism in metabolism
• Endothelial dysfunction
Metabolism of purines and ddI

- Hypoxanthine
- Xanthine
- Uric acid
- Purine
- Nucleoside
- Phosphorylase
- Xantine Oxidase
- ddI
- ddA
- ddA-TP
- ddA-DP
- ddA-MP
- ddI-MP
- ATP
- ADP
- AMP
- A.Succinate
- Inosine
- Inosine-MP
- XMP
- GMP
- GDP
- GTP
- DNA, RNA
- Guanosine
- Adenylosuccinate Synthetase
- Adenylosuccinate Lyase
- Nucleoside Diphosphate Kinase
- Adenylate Kinase
- Adenylate Phosphorylase
- Guanylate Kinase
- Nucleoside Diphosphate Kinase
- DNA, RNA
- Ribose 5-phosphate
- 5-Phosphoribosyl 1-pyrophosphate
- guanylate kinase
- guanosine triphosphate kinase
- guanosine monophosphate
- guanosine diphosphate
- guanosine triphosphate

**Enzymes and Reactions:**
- 5’Nucleotidase
- Adenylosuccinate Synthetase
- Adenylosuccinate Lyase
- Inosine Triphosphatase
- Guanylate Kinase
- ADP
- ATP
- AMP
- ddA
- ddI

**Key Phosphates:**
- MP: monophosphate
- DP: diphosphate
- TP: triphosphate
- XMP: xanthosine monophosphate
- GMP, GDP, GTP: guanosine mono-, di-, tri- phosphate.
- AMP, ADP, ATP: adenosine mono-, di-, tri- phosphate.
- ddI: didanosine
- ddA: dideoxiadenosine
Objectives

• To investigate the impact of polymorphisms at genes coding enzymes involved in purine metabolic pathway

• To understand the role of genetic background in the development of NCPH

Hypothesis: We hypothesized that some metabolites emerging during ddl metabolism might cause damage in the endothelium of portal vessels.
Methods

- Descriptive case-control study

- The two groups were matched by:
  - Length of ddI exposure,
  - Age
  - Gender

- Tagging SNPs at 4 enzymes (was performed using SNPlex microarray)
  - inosine triphosphatase
  - 5’-nucleotidase cytosolic II
  - purine nucleoside phosphorylase
  - xanthine oxidase

- Exclusion criteria:
  - Coinfection with hepatitis C/B
  - Alcohol abuse
  - Evidence of liver cirrhosis
Metabolism of purines and ddI

MP: monophosphate
DP: diphosphate
TP: triphosphate
XMP: xanthosine monophosphate
GMP, GDP, GTP: guanosine mono-, di-, tri- phosphate.
AMP, ADP, ATP: adenosine mono-, di-, tri- phosphate.
ddi: didanosine
ddA: dideoxiadenosine
## Results 1

### Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (range)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients [n (M/F)]</td>
<td>80 (53/27)</td>
</tr>
<tr>
<td>Case/Control</td>
<td>22/58</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>47 (44-53)</td>
</tr>
<tr>
<td>ddl exposure (months)</td>
<td>66 (48-86)</td>
</tr>
<tr>
<td>Total SNPs analysed</td>
<td>36</td>
</tr>
</tbody>
</table>

*unless differently specified*
Genetic polymorphisms influencing the risk of NCPH in HIV

<table>
<thead>
<tr>
<th>rs11191561</th>
<th>CC</th>
<th>CG/GG</th>
<th>53</th>
<th>27</th>
<th>9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11598702</td>
<td>TT</td>
<td>TC/CC</td>
<td>32</td>
<td>48</td>
<td>9%</td>
</tr>
</tbody>
</table>

- rs11191561: 9/13 (17%)
- rs11598702: 3/19 (9%)

p=0.007
Genetic polymorphisms influencing the risk of NCPH in HIV

- **5-nucleotidase**
  - rs11191561: 17% CC, 48% CG/GG, 9% TT, 40% TC/CC
  - rs11598702: 9% CC, 13% CG/GG, 9% TT, 19% TC/CC

- **Xantin-oxidase**
  - rs1429376: 71% AA, 23% AC/CC
  - rs1594160: 71% AA, 23% AC/CC

*p-values reported:*
- rs11191561: 0.007
- rs11598702: 0.007
- rs1429376: 0.015
- rs1594160: 0.015
Conclusions

• SNPs at the 5’-nucleotidase and xanthine oxidase genes influence the risk of developing NCPH

• Endothelial damage at portal vessels caused by increased levels of harmful purine metabolites of ddI

• Descriptive study, might not influence the clinical management at this stage
## Acknowledgements

**Hospital Carlos III, Madrid, Spain**  
Dr Vicente Soriano  
Judit Morello  
Eugenia Vispo  
Elena Alvarez  
Sonia Rodriguez-Novoa  

**University of Bonn, Bonn, Germany**  
Dr Juergen Rockstroh  
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