Introduction
• 15-20 million people are infected worldwide with chronic hepatitis D (HDV).
• Up to 80% of patients with HDV may develop cirrhosis within 5-10 years.
• Interferon-based therapy is unsatisfactory, <30% achieve HBsAg loss and become HDV RNA negative.
• Nucleoside/tide analogues are ineffective.
• Prenylation inhibition has demonstrated effectiveness against HDV in in vitro & in vivo models.

Aims
• To assess the antiviral effect and safety of the prenylation inhibitor, lonafarnib, in patients with chronic HDV infection.

Methods
• 14 chronically infected HDV patients were sequentially enrolled into 2 groups in a phase 2a double-blinded, randomized, placebo-controlled study.
• Serial measurements of safety parameters, liver tests, virologic (HDV RNA & HBV DNA) markers and symptom questionnaires were performed.

Results

Table 1: Patient Demographics

<table>
<thead>
<tr>
<th>Feature</th>
<th>Placebo</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Placebo vs Group 1</th>
<th>Placebo vs Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>71%</td>
<td>77%</td>
<td>77%</td>
<td>0.58</td>
<td>0.58</td>
</tr>
<tr>
<td>Median Age</td>
<td>38</td>
<td>36</td>
<td>36</td>
<td>0.34</td>
<td>0.5</td>
</tr>
<tr>
<td>Caucasian</td>
<td>43%</td>
<td>46%</td>
<td>46%</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>Asian</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>African</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Median Baseline History</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 2: Baseline Lab Values

<table>
<thead>
<tr>
<th>Feature</th>
<th>Placebo</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Placebo vs Group 1</th>
<th>Placebo vs Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (IU/L)</td>
<td>32</td>
<td>33</td>
<td>33</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>103</td>
<td>103</td>
<td>103</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>T. Bili (mg/dL)</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Discussion
• After 28 days of therapy with lonafarnib, serum HDV RNA was significantly lower in both treatment groups compared to placebo.
• A dose dependent reduction in serum HDV RNA was seen with lonafarnib therapy.
• Serum lonafarnib concentrations correlate with HDV RNA decline.
• No HDV resistance was identified.
• Lonafarnib was safe and generally well tolerated at the prescribed doses for 28 days.

Conclusion
• This is the first demonstration that treatment of chronic HDV with the prenylation inhibitor lonafarnib significantly reduces virus levels in patients.
• The decline in virus levels significantly correlated with serum drug levels, providing further evidence for the efficacy of prenylation inhibition in chronic HDV.

References

Disclosures
• This work was supported by the Intramural research programs of the NIDDK, NCI & NICHD, NIH.
• All patients provided informed consent for IRB approved studies.
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