Effect of ANG-3070 in the Passive Heymann’s Nephritis Rat Model of Primary Proteinuric Kidney Disease

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Disclosures

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Background

- Primary proteinuric kidney diseases (PPKD) as a group are an important cause of end-stage kidney disease (ESKD)
- Many receptor tyrosine kinases, including platelet-derived growth factor receptor (PDGFR), contribute to the progression of PPKDs to ESKD;¹ elevated expression of PDGFR ligands have been implicated in progressive glomerulonephritis²
- ANG-3070 is a novel inhibitor of multiple tyrosine kinases, including PDGFRα/β, and DDR1/2³
- The Passive Heymann Nephritis (PHN) model of renal dysfunction mimics immune complex disease due to podocyte-targeting antibodies, and is reminiscent of human membranous nephropathy and glomerulonephritis with nearly identical pathology⁴,⁵
  - In this model, intravenous administration of anti-FX1A serum to rats results in immune complex accumulation, slit diaphragm occlusion, podocyte foot process effacement, and proteinuria⁴

Objective: To evaluate the effects of ANG-3070 in a rat model of proteinuric PHN

Methods

- CD rats received anti-FX1A serum or saline on two consecutive days.
- Animals were randomized based on proteinuria levels, ensuring equivalent average protein to creatinine ratios (PCR) in each group, before beginning treatment.
- Nintedanib, a tyrosine kinase inhibitor that targets PDGFRα/β, FGFR1-3, and VEGFR1-3, was used as a comparator.
- Glomerular injuries were evaluated from periodic acid Schiff-stained kidneys on a scale of 0 (normal/no injury) to 4 (severe injury) by two observers and averaged.
- One-way analysis of variance with Tukey’s multiple comparisons test was used to determine significant differences among groups.
ANG-3070 treatment did not reduce survival

- No significant differences in survival among the sham, Vehicle, and ANG-3070 (all doses) groups.

- Survival was significantly decreased in the Nintedanib group versus sham and Vehicle Cohorts ($P<0.01$, Mantel-Haenszel Log Rank Test).

- Body mass and kidney mass were significantly reduced in Nintedanib-treated animals compared with Vehicle controls ($P<0.0001$), but there were no differences in body mass or kidney mass with ANG-3070 versus Vehicle or sham (data not shown).

1. Sham and vehicle curves are not visible as they are identical to the 15 mg/kg ANG-3070 group.
ANG-3070 reduced proteinuria

- Mean PCR at the end of the study was significantly reduced for the ANG-3070 100 mg/kg ($P=0.04$) and 15 mg/kg group ($P=0.05$), but not for the ANG-3070 50 mg/kg and Nintedanib group compared with Vehicle.
ANG-3070 reduced kidney fibrosis and glomerular damage

**Kidney Fibrosis**

(Dealing score is better)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sham</th>
<th>Vehicle</th>
<th>15 mg/kg</th>
<th>50 mg/kg</th>
<th>100 mg/kg</th>
<th>Nintedanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg Hydroxyproline per kidney (SEM)</td>
<td>1600 ± 100</td>
<td>1500 ± 100</td>
<td>1400 ± 100</td>
<td>1300 ± 100</td>
<td>1200 ± 100</td>
<td>1100 ± 100</td>
</tr>
</tbody>
</table>

**Glomerular Damage**

(Dealing score is better)

<table>
<thead>
<tr>
<th>Group</th>
<th>Sham</th>
<th>Vehicle</th>
<th>15 mg/kg</th>
<th>50 mg/kg</th>
<th>100 mg/kg</th>
<th>Nintedanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular damage score (SEM)</td>
<td>4.5 ± 0.5</td>
<td>4.0 ± 0.5</td>
<td>3.5 ± 0.5</td>
<td>3.0 ± 0.5</td>
<td>2.5 ± 0.5</td>
<td>2.0 ± 0.5</td>
</tr>
</tbody>
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* P<0.05 Sham vs All groups; # Nintedanib vs All groups
ANG-3070 reduced expression of PDGFRβ in kidney

- Induction of PHN was associated with an increase in PDGFRβ expression, which was significantly reduced with ANG-3070 treatment (P=0.04)
Pharmacokinetics of repeated doses

- Blood concentration over time shows two distinct peaks potentially indicating entero-hepatic recirculation of ANG-3070.
- C_{max} exposure to ANG-3070 increased in a greater than dose-proportional manner: a 3.3-fold and a 2.0-fold increase in dose resulted in approximately a 4.8-fold and 2.0-fold increase in C_{max}, respectively.
Conclusions

- ANG-3070 reduced proteinuria, renal fibrosis, glomerulosclerosis, and PDGFRβ expression levels in a rat model of membranous nephropathy.
- The lowest dose tested (15 mg/kg) had the lowest drug exposure and was sufficient to elicit the beneficial effects of ANG-3070.

Key Takeaway: These data suggest that twice-daily oral administration of the novel tyrosine kinase inhibitor ANG-3070 may be an effective treatment in PPKDs.