APL-2, a complement C3 inhibitor, may potentially reduce both intravascular and extravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria

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BACKGROUND

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, potentially life-threatening disease characterized by complement-mediated hemolytic anemia.
- PNH arises from a somatic mutation resulting in impairment of an anchor protein responsible for the expression of numerous proteins at the cell surface of the red blood cells, including CD55 and CD59, two complement inhibitory proteins.
- Subsequent uncontrolled activation of the complement system leads to both intravascular and extravascular hemolysis, or cell opsonization, mediated by C3b accumulation at the cell surface.
- Due to the key position of C3 in the complement cascade, APL-2, a PEGylated cyclic peptide inhibitor of C3, may prevent both intravascular and extravascular hemolysis and could therefore be potential treatment for PNH.

AIM

To assess safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of multiple doses of APL-2 given as monotherapy in patients with PNH.

STUDY DESIGN

- Cohort 1: Two subjects. APL-2: 180 mg/mL.
- Cohort 2: Three subjects. APL-2: 270 mg/mL.
- Daily subcutaneous injection of APL-2 for 4 weeks (Cohort 1) and up to a year (cohort 2).

ENTRY CRITERIA

- Healthy male or female aged 18-55 years.
- Eculizumab-naïve subjects.
- Blood transfusion in the prior 12 months.
- Lactate dehydrogenase (LDH) levels ≥ 2 times the upper limit of normal (ULN).
- All subjects received vaccination against N. Meningitides, S. pneumoniae and H. influenza and commenced prophylactic oral antibiotics.

RESULTS

Cumulative Adverse Event Review

<table>
<thead>
<tr>
<th>Variable/Preferred Term/OC</th>
<th>Severity</th>
<th>Action taken</th>
<th>Relationship to study drug</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site erythema (3 months)</td>
<td>Minor</td>
<td>None</td>
<td>Not related</td>
<td>Recovered</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>Minor</td>
<td>Antibiotics, -</td>
<td>Not related</td>
<td>Recovered</td>
</tr>
<tr>
<td>Possible allergic reaction</td>
<td>Minor</td>
<td>Not related</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Nose Bleed</td>
<td>Minor</td>
<td>None</td>
<td>Not related</td>
<td>Recovered</td>
</tr>
<tr>
<td>Gums Bleed</td>
<td>Minor</td>
<td>None</td>
<td>Not related</td>
<td>Recovered</td>
</tr>
<tr>
<td>Injection site erythema 2</td>
<td>Minor</td>
<td>None</td>
<td>Not related</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

A. LDH levels

![LDH levels graph](image)

A. PNH Type II + Type III cells

![PNH Type II + Type III cells graph](image)

B. C3 deposition on type II + type III cells

![C3 deposition graph](image)

CONCLUSIONS

- Daily subcutaneous injection of APL-2 is safe and well-tolerated at 180 and 270 mg/d.
- APL-2 in mono-therapy led to a sustained suppression of hemolysis with evidence of dose-response an increased proportion of PNH Type II and III RBCs, and a decreased C3 deposition.
- These data support the hypothesis that C3 inhibition may prevent both intravascular and extravascular hemolysis.
- APL-2 is the first C3 inhibitor tested in patients with PNH. APL-2 might help transfusion-dependent patients become transfusion-independent and might stabilize hemoglobin levels.