Emicizumab (HEMLIBRA) is a bivalent humanized monoclonal antibody that is approved in the United States for prophylactic treatment of patients with hemophilia A (FVIII) with inhibitors, with ongoing clinical trials in FVIII without inhibitors.

Emicizumab restores missing activated factor VIII (FVIIIa) function by bridging FVIIIa and FIX to facilitate effective hemostasis (Figure 1).

**Figure 1: Emicizumab mechanism of action**

In the primary analysis (clinical cohort, October 25, 2015) of the multinational, randomized, phase 3 HAVEN 1 study (NCT02822322) in FVIIIa with inhibitors aged ≥12 years:

- Emicizumab prophylaxis in no prophylaxis significantly reduced annualized bleeding rate (treated bleeds) by 87% (95% CI: 56%–100%).
- A total of 62.9% vs 15.5% of patients experienced severe treated bleeds with emicizumab prophylaxis vs no prophylaxis, respectively.

During the study, serious thrombotic and thrombotic microangiopathy (TMA) events were reported in 5 patients (1 of those patients after primary analysis clinical cohort) and were associated with activated protein C thrombin complex (APCC) doses ≥100 U/kg/day given for >24 hours for treatment of breakthrough bleeds (BTT) during emicizumab prophylaxis.

- No events were reported when emicizumab was given alone, or in conjunction with recombinant FVIIIa (rFVIIa) alone.

To mitigate further risk of thrombotic TMA events, the approach implemented dosing guidance to study investigators for bypassing agent (BPA) use during emicizumab prophylaxis.

We describe changes in BPA use in HAVEN 1 pre and post BPA dosing guidance during emicizumab prophylaxis.

**METHODS**

All patients of HAVEN 1: patients were instructed to treat BTTs with BPAs according to the standard of care, based on the emicizumab and emicizumab + BPA safety profiles seen in the phase 1/2 study.

With the emerging TMA and thrombotic events, guidance provided on BPA use during emicizumab prophylaxis:

- Exercise caution when using rFVIIa.
- Avoid the use of aPCC.
- If aPCC is the only available BPA, use of the lowest dose expected to achieve hemostasis with the initial dose ≥50 U/kg.
- BTBs should preferably be treated with the lowest rFVIIa dose expected to achieve hemostasis, using ≥90 µg/kg/day in the initial dose.
- Perform local laboratory assessments to monitor for the risk of TMA or thrombotic events; a central laboratory will analyze samples post-hoc for confirmation.

**RESULTS**

Data were analyzed as of the cutoff date, April 21, 2017.

- Median (range) emicizumab exposure duration was comparable for pre (187.0 [30–336] weeks) and post (160.3 [28–189] weeks) dosing guidance during BPA use periods.

APCC treatment episodes:

- There were 63 APCC treatment episodes in 19 patients pre-dosing guidance, and 15APCC treatment episodes in 5 patients post-dosing guidance (Figure 1, Table 2).

Post dosing guidance:

- The majority of APCC treatment episodes were ≤50 U/kg/day and consistent with 1 injection only: 43 (68.3%) treatment episodes were ≤24 hours (Table 1).
- Of 19 (30.2%) treatment episodes ≥100 U/kg/day, 7 (11.1%) treatment episodes were >24 hours (Table 1).

- Of those 7 treatment episodes were associated with the reported TMA/thrombotic events (Figure 2).

Post dosing guidance:

- The majority of APCC treatment episodes were ≤50 U/kg/day and consistent with 1 injection only: 43 (68.3%) treatment episodes were ≤24 hours (Table 1).
- Of 19 (30.2%) treatment episodes ≥100 U/kg/day, 7 (11.1%) treatment episodes were >24 hours (Table 1).

This patient subsequently experienced a TMA event.

The 3 treatment episodes associated with THMA/thrombotic events (4 occurring pre and 1 post dosing guidance) are shown in Figure 3.

**Table 1: Treatment episodes per average daily exposure of APCC pre and post dosing guidance**

<table>
<thead>
<tr>
<th>Average daily dose of APCC</th>
<th>Number of treatment episodes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre dosing guidance (19 patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50 U/kg/day</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;50 U/kg/day</td>
<td>19</td>
<td>1.000</td>
</tr>
</tbody>
</table>

- There were 51/61 treatment episodes in 25 patients pre-dosing guidance, and 49 treatment episodes in 19 patients post dosing guidance (Table 2, Figure 2).

- The majority of APCC treatment episodes were ≤50 U/kg/day and consistent with 1 injection only: 43 (68.3%) treatment episodes were ≤24 hours (Table 2).

- Of 19 (30.2%) treatment episodes ≥100 U/kg/day, 7 (11.1%) treatment episodes were >24 hours (Table 2).

- Post dosing guidance: 25 (33.3%) treatment episodes were >270 µg/kg/day (Table 2).

- Post dosing guidance: 3 (6.1%) treatment episodes were >270 µg/kg/day (Table 2).

**Table 2: Treatment episodes per average daily exposure of APCC pre and post dosing guidance**

<table>
<thead>
<tr>
<th>Average daily dose of APCC</th>
<th>Number of treatment episodes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre dosing guidance (29 patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50 U/kg/day</td>
<td>42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;50 U/kg/day</td>
<td>19</td>
<td>1.000</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

- Dosing guidance implemented for BPA treatment during emicizumab prophylaxis in the HAVEN 1 study led to a decrease in the number of patients who used aPCC, with most switching to rFVIIa.

- Of 51/61 patients were not exposed to BPA use during emicizumab prophylaxis, due to lack of bleeds requiring treatment.

- Following dosing guidance, lower doses of aPCC and rFVIIa were used to treat or prevent BTBs in patients who used emicizumab prophylaxis.

- Further TMA/thrombotic events were successfully mitigated when dosing guidance was followed in ≥90% of patients with inhibitors in the emicizumab development program to date.

**ACKNOWLEDGMENTS AND DISCLOSURES**

- The authors report disclosures in full in the Supplementary Material.

**REFERENCES**


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