Use of Bypassing Agents Prior to and Post Bypassing Agent Dosing Guidance During Emicizumab Prophylaxis: Analyses from the HAVEN 1 Study

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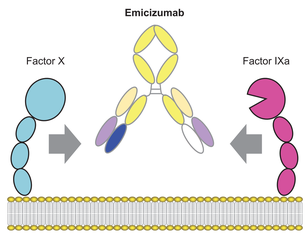
INTRODUCTION

- Emicizumab (HEMLIBRA®) is a bispecific humanized monoclonal antibody[1] that is approved in the United States for prophylactic treatment of persons with hemophilia A (PwHA) with inhibitors, with ongoing clinical trials in PwHA without inhibitors
- Emicizumab restores missing activated factor VIII (FVIIIa) function by bridging FIXa and FX to facilitate effective hemostasis[2] (**Figure 1**)

Figure 1: Emicizumab mechanism of action



- In the primary analysis (clinical cutoff, October 25, 2016) of the multicenter, randomized, phase 3 HAVEN 1 study (NCT0262232) in PwHA with inhibitors aged ≥12 years[3]:
  - Emicizumab prophylaxis vs no prophylaxis significantly reduced annualized bleeding rate (treated bleeds) by 87% (P<0.001)
  - A total of 62.9% vs 5.6% of patients experienced zero 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 these patients after primary analysis clinical cutoff) and were associated with activated prothrombin complex concentrate (aPCC) doses >100 U/kg/day given for ≥24 hours for treatment of breakthrough bleeds (BTBs) during emicizumab prophylaxis
    - No events were reported when emicizumab was given alone, or in conjunction with recombinant FVIIa (rFVIIa) alone
    - To mitigate further risk of thrombotic TMA events, the sponsor 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

- At the onset of HAVEN 1, patients were instructed to treat BTBs with BPAs according to standard of care, based on the emicizumab and emicizumab + BPA safety profiles seen in the phase 1/2 study[4]
- With the emerging TMA and thrombotic events, guidance provided on BPA use during emicizumab prophylaxis advised:
  - 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 as the initial dose
  - Perform local laboratory assessments to monitor for the risk of TMA or thromboembolic 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 (167.0 [20–334] weeks) and post (168.3 [28–186] weeks) dosing guidance for BPA use periods

aPCC treatment episodes

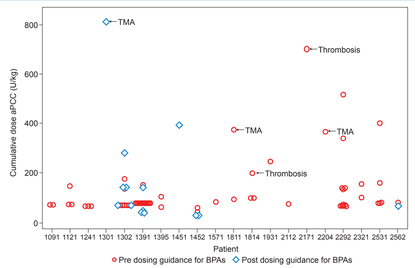
- There were 63 aPCC treatment episodes in 18 patients pre dosing guidance, and 15 aPCC treatment episodes in 6 patients post dosing guidance (**Table 1, Figure 2**)
- Pre dosing guidance:
  - The majority of aPCC treatment episodes were ≤100 U/kg/day and consistent with 1 injection only; 43 (68.3%) 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**)
    - 4 of those 7 treatment episodes were associated with the reported TMA/thrombotic events (**Figure 2**)
- Post dosing guidance:
  - There were 6 (40.0%) treatment episodes <50 U/kg/day and 7 (46.7%) treatment episodes 50–100 U/kg/day, 9 of 13 for ≤24 hours (**Table 1**)
  - Of 2 (13.3%) treatment episodes that were >100 U/kg/day, 1 treatment episode was ≥24 hours (**Table 1**)
    - This patient subsequently experienced a TMA event
- The 5 treatment episodes associated with TMA/thrombotic events (4 occurring pre and 1 post dosing guidance) are shown in **Figure 2**

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

Duration (24-hour intervals) of aPCC treatment	Average daily dose of aPCC (U/kg/day)				Total number of treatment episodes per 24 hours
	<50	50–100	101–150	>150	
Pre dosing guidance (18 patients)					
Day 1	1	42	7	5	**55**
Day 2	0	1	1	0	**2**
Day 3	0	0	3	1	**4**
Day 4	0	0	2	0	**2**
Day >4	0	0	0	0	**0**
Total number of treatment episodes per average daily dose category	1	43	13	6	**63**
Post dosing guidance (6 patients)					
Day 1	5	4	1	0	**10**
Day 2	0	2	0	0	**2**
Day 3	0	0	0	0	**0**
Day 4	0	1	0	1	**2**
Day >4	1	0	0	0	**1**
Total number of treatment episodes per average daily dose category	6	7	1	1	**15**

aPCC, activated prothrombin complex concentrate

Figure 2: Maximum cumulative dose of aPCC per treatment episode pre and post dosing guidance during emicizumab prophylaxis



Pre dosing guidance, 63 treatment episodes in 18 patients; post dosing guidance, 15 treatment episodes in 6 patients
aPCC, activated prothrombin complex concentrate; BPA, bypassing agent; TMA, thrombotic microangiopathy

rFVIIa treatment episodes

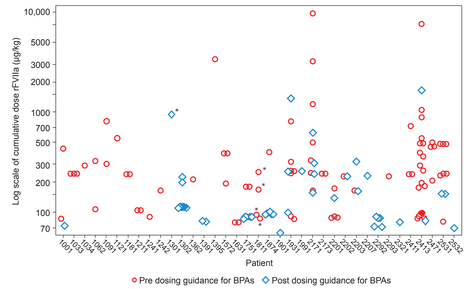
- There were 91 rFVIIa treatment episodes in 28 patients pre dosing guidance, and 49 treatment episodes in 19 patients post dosing guidance (**Table 2, Figure 3**)
- Pre dosing guidance, the majority (56 [61.5%]) of rFVIIa treatment episodes were ≤270 µg/kg/day for ≤24 hours (**Table 2**)
- Pre dosing guidance, 23 (25.3%) 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 rFVIIa pre and post dosing guidance

Duration (24-hour intervals) of a rFVIIa treatment	Average daily dose of rFVIIa (µg/kg/day)				Total number of treatment episodes per 24 hours
	<50	50–180	181–270	>270	
Pre dosing guidance (28 patients)					
Day 1	11	19	26	14	**70**
Day 2	1	2	6	5	**14**
Day 3	0	1	1	0	**2**
Day 4	0	0	0	0	**0**
Day >4	0	0	1	4	**5**
Total number of treatment episodes per average daily dose category	12	22	34	23	**91**
Post dosing guidance (19 patients)					
Day 1	12	24	7	1	**44**
Day 2	0	1	0	1	**2**
Day 3	0	0	1	0	**1**
Day 4	0	0	0	0	**0**
Day >4	0	0	1	1	**2**
Total number of treatment episodes per average daily dose category	12	25	9	3	**49**

rFVIIa, recombinant activated factor VII

Figure 3: Maximum cumulative dose of rFVIIa per treatment episode for pre and post dosing guidance during emicizumab prophylaxis

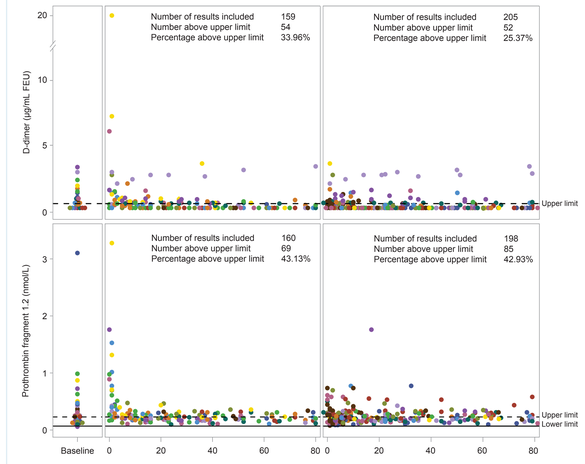


Pre dosing guidance, 91 treatment episodes in 28 patients; post dosing guidance, 49 treatment episodes in 19 patients
*Doses in the time frame of thrombotic microangiopathy event
BPA, bypassing agent; rFVIIa, recombinant activated factor VII

Laboratory assessments

- Levels of both prothrombin fragment (PF) 1.2 and D-dimer were elevated in some patients, but not all, within the first 24–48 hours after a dose of aPCC but not after a dose of rFVIIa (**Figure 4**)
  - The elevation was not correlated to amount of aPCC administered (data not shown)
  - Elevated values also occurred sporadically throughout the study, not associated with BPA use
  - The lack of change after rFVIIa administration may be due to the lack of sampling within the half-life of rFVIIa (~2–6 hours)[5]
- Elevated PF1.2 and D-dimer values also were seen in multiple patients at the baseline visit, before the first dose of emicizumab, possibly due to BPA use within 48 hours of baseline sample collection

Figure 4: Central laboratory values for D-dimer and prothrombin fragment 1.2, as a function of time since last dose of BPA



Baseline is the last available result before emicizumab treatment start
All other results are during emicizumab prophylaxis
Only patients with ≥1 lab test done within 72 hours after rFVIIa or aPCC treatment are included
Data points are colored according to patient ID; 1 patient (lavender dots) had consistently elevated D-dimer values at baseline and throughout the study, regardless of emicizumab or BPA use
aPCC, activated prothrombin complex concentrate; BPA, bypassing agent; rFVIIa, recombinant activated factor VII

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
- Over 60% of 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 on emicizumab prophylaxis
  - In the third TMA case, which occurred post dosing guidance, the guidance was not followed
- Further TMA/thrombosis events were successfully mitigated when dosing guidance was followed in >200 PwHA with inhibitors in the emicizumab development program to date

ACKNOWLEDGMENTS AND DISCLOSURES

Editorial assistance for this poster was provided by Samantha Taylor, PhD, of Envision Pharma Group, and funded by F. Hoffmann-La Roche Ltd

MUC: speaker bureau (Baxalta, Novo Nordisk, Roche/Genentech, Inc., Shire), shareholder (Alnylum), advisory panel (Baxalta, Bayer, Biogen, Bioveritiv, CSL Behring, Grifols, Pfizer, Octapharma, Roche/Genentech, Shire), grant/research support (Global Blood Therapeutics, Pfizer, Roche/Genentech, Inc., Sancilio); **CN:** grant/research support (Alnylam, Baxalta/Shire, Bayer, Biogen/Sobi, CSL Behring, Novo Nordisk, Octapharma, Pfizer), speaker bureau (Baxalta/Shire, Bayer, Biogen/Sobi, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche); **GY:** consultant (Alnylam, Bayer, Bioverativ, CSL Behring, Genentech, Inc., Kedrion, Novo Nordisk, Roche, Shire); **LK:** honoraria (Baxalta/Shire); **JM:** consultant/advisory committee (Alnylam, Baxalta, Biogen, CSL Behring, Novo Nordisk, Roche, Shire), grant/research support (Alnylam, Bayer, Biogen, Catalyst Biosciences, CSL Behring, Novo Nordisk, Roche), speaker bureau (Alnylam, Amgen, Bayer, Biogen, Biotest, CLS Behring, Roche); **JW:** grant/research support (Baxalta, Bayer, Biogen, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Shire), consultant (Baxalta, Bayer, Biogen, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Shire); **JO:** consultancy (Baxalta, Baxter, Bayer, Biogen, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi), speaker bureau (Baxalta, Baxter, Bayer, Biogen, Biotest, Chugai, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi), research funding (Baxalta. Baxter, Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma); **DN, JX, JA:** employee (Genentech, Inc.); **OC, EA:** employee (Roche); **MS**. grant/research support (Baxalta, Bayer, Chugai, CSL Behring, Novo Nordisk, Pfizer), consultant (Baxalta, Bayer, Biogen, Chugai, CSL Behring, Kaketsuken, Novo Nordisk, Pfizer), speaker bureau (Baxalta, Chugai)

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Presented at the 59th American Society of Hematology Annual Meeting & Exposition I Atlanta, GA I December 9–12, 2017