Long-term efficacy and safety of subcutaneous concizumab prophylaxis in hemophilia A and hemophilia A/B with inhibitors. Amy D. Shapiro et al.

Supplementary Materials

Methods

Treatment regimen

Patients in both trials received daily subcutaneous injections of 0.15 mg/kg concizumab, with potential dose escalation to 0.20 or 0.25 mg/kg. In the explorer4 trial, an initial loading dose of 0.5 mg/kg concizumab was administered, whereas patients enrolled in explorer5 did not receive a loading dose. Dose escalation criteria were ≥3 treatment-requiring spontaneous bleeding episodes within 12 weeks whilst receiving concizumab throughout both trials.

Patient visits took place at Weeks 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 44 and 48; and then every 8 weeks until end of treatment during explorer4 (with a follow-up visit 8 weeks after the last week of treatment). In the explorer5 trial, patient visits took place at Weeks 1, 4, 8, 12, 16, 20, 24, 32, 40, and 48; and then every 8 weeks until end of treatment (with a follow-up visit 8 weeks after the last week of treatment). Patients were monitored for criteria for premature discontinuation, bleeding episodes, adverse events, and blood samples were taken at all visits (with the exception of the Week 1 visit in the explorer5 trial, when blood samples were not taken).

Supportive medications

Breakthrough bleeding episodes requiring treatment were managed with recombinant activated factor VII (rFVIIa) in explorer4 (providing there were no safety concerns following the dose delivered in a non-bleeding state as described above) and with non-modified FVIII in explorer5.

Criteria for discontinuation

Discontinuation criteria for concizumab treatment were inclusion in the trials in violation of inclusion/exclusion criteria or randomization criteria, simultaneous participation in another clinical trial, incapacity or unwillingness to follow trial procedures, anaphylactic reaction, thromboembolic event, event of disseminated intravascular coagulation, lack of efficacy due to neutralizing antibodies, lack of efficacy defined as ≥3 treated bleeding episodes within the previous 12 weeks in patients treated at the highest dose level (0.25 mg/kg), and withdrawal of patient consent. An additional discontinuation criterion in explorer5 was development of inhibitors to factor VIII (≥0.6 Bethesda units).

Independent data monitoring committee

The members of the independent data monitoring committee were:

- Erik Berntorp (committee chair); Lund University, Sweden
- Marcel Levi (committee member); University College London Hospitals, UK and Amsterdam University Medical Center, Netherlands
- Thomas Abshire (committee member); Versiti, Milwaukee, Wisconsin, USA
- Victor De Gruttola (committee member/statistician); Harvard TH Chan School of Public Health, Boston, USA
- Fan-fan Yu (independent statistician); Statistics Collaborative, Inc., USA
- Lijuan Zeng (independent statistician); Statistics Collaborative, Inc., USA

Results

Impact of COVID-19 on explorer5

Due to the impact of the COVID-19 pandemic, some patients were unable to attend the last visit (Visit 16) at the study site the day after the final concizumab dose as per-protocol requirements. For affected patients, the number of days between final dose and Visit 16 ranged from 1–45. Five patients had Visit 16 converted to a phone call, and the last patient

completed the trial in June 2020. Overall, the COVID-19 pandemic did not affect the endpoints of the trial as all patients had already received at least 76 weeks of treatment with concizumab. No safety concerns were observed due to the pandemic, and the trial data were acceptable for interpretation.

Safety

Adverse events

During the main + extension parts of explorer4, two patients temporarily discontinued treatment. One patient had an interruption of 13 days whilst receiving 0.15 mg/kg concizumab due to events of both D-dimer increase and prothrombin fragment 1+2 increase (mild and assessed as probably related to treatment), and restarted treatment following their recovery from these events. Another patient receiving 0.15 mg/kg required surgery for bone fractures in the hand following an accident, and subsequently had a pause in concizumab treatment for 50 days. Two days after the surgery, this patient had a severe femoral arterial puncture bleed leading to hemorrhagic shock. Seven weeks later, the patient restarted concizumab treatment. The ADA titer for this patient increased to high levels with a neutralizing effect *in vitro,* and an *in vivo* effect was demonstrated by normalization of free TFPI to baseline levels. Despite this, the patient continued treatment with concizumab for a further 7 months and experienced one mild/moderate treated bleed. Seven months after resumption of treatment, the patient experienced an event of subdural hemorrhage and muscle hemorrhage following a fall, which were severe and judged as unlikely to be related to concizumab treatment. After hospitalization for these events, concizumab treatment was temporarily discontinued, and the patient was later discharged from hospital. The patient continued to be positive for ADAs (see the Immunogenicity section for more details) and treatment was permanently discontinued due to suspicion of no therapeutic effect with restoration of free TFPI.

Concizumab treatment was temporarily discontinued in three patients in the explorer5 trial. One of these patients missed their 0.15 mg/kg dose on 1 day due to an AE of gastrointestinal

infection (assessed as unlikely to be related to concizumab treatment). Another patient (also receiving 0.15 mg/kg concizumab) had a treatment interruption of 10 days due to an event of episcleritis. This was assessed as possibly related to treatment, and concizumab was resumed after the patient had recovered from the event. Following events of elevation of prothrombin fragment 1+2 and D-dimers (judged as probably related to concizumab), a third patient had their 0.25 mg/kg dose interrupted for 12 days. Dosage was subsequently lowered to 0.20 mg/kg in this patient due to the D-dimer increase, with a later re-escalation to 0.25 mg/kg. The same patient later experienced a serious event of atypical pneumonia (assessed as possibly related to treatment) whilst receiving 0.25 mg/kg concizumab, resulting in a 41-day interruption of treatment before resuming after the patient had recovered.

Supplementary Tables and Figures

Supplementary Table 1. Annualized bleeding rates during the entire exposure period of the main + extension parts of explorer4 (HAwI, HBwI) and explorer5 (HA); full analysis set.

	explorer4 (N=25)	**explorer5 (N=36)**
Number of treated bleeding episodes	256	464
Cumulative concizumab exposure time, years	44.8	68.2
Estimated mean ABR (95% CI)	5.7 (4.2–7.8)	9.9 (6.6–14.7)
Estimated mean spontaneous bleed ABR (95% CI)	3.1 (2.3–4.3)	4.9 (3.2–7.5)

Least-squares mean estimates of ABR (95% confidence interval) are shown. The ABR estimate was based on a negative binomial regression with log of exposure time as offset. ABR, annualized bleeding rate; CI, confidence interval; HA, hemophilia A without inhibitors; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors.

Supplementary Table 2. Annualized bleeding rates on the last concizumab dose level of patients who received on-demand treatment with rFVIIa during the main part and concizumab treatment during the extension part of explorer4 (HAwI, HBwI).

	On-demand rFVIIa (N= 8)	**Concizumab prophylaxis (N=8)**
Estimated mean ABR* (95% CI)	18.6 (12.9–26.9)	4.9 (2.2–10.6)
Estimated mean spontaneous bleed ABR* (95% CI)	16.9 (11.2–25.5)	2.5 (1.0–6.2)
Estimated mean joint bleed ABR* (95% CI)	13.8 (9.6–19.9)	2.9 (1.1–7.7)

*LS means estimates of ABR. ABR was estimated based on a negative binomial regression with log-exposure time as offset and treatment regimen as a factor, and within-subject correlation was estimated using a generalized estimating equation analysis, with working independence covariate structure and using a robust estimator.
ABR, annualized bleeding rate; CI, confidence interval; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; LS, least squares; N/A, not available; rFVIIa, activated recombinant Factor VII.

Supplementary Table 3. Peak thrombin generation during the main + extension parts of explorer4 (HAwI, HBwI) and explorer5 (HA); full analysis set.

	explorer4 (N=25)		explorer5 (N=36)	
Peak thrombin generation prior to last dose (nmol/mL)*	**n****	**Mean (SD)**	**n*****	**Mean (SD)**
Concizumab dose:				
0.15 mg/kg	11	79.5 (55.3)	13	90.8 (45.2)
0.20 mg/kg	9	98.7 (20.4)	10	99.1 (36.2)
0.25 mg/kg	3	75.7 (30.6)	7	111.6 (63.5)

*Normal reference range: 26–147 nmol/L.
**Two patients who withdrew with a long period between their last dose and their last visit at site were not included in these numbers. ***n was the number of patients with available values at visit. HA, hemophilia A without inhibitors; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; SD, standard deviation.

Supplementary Table 4. Treatment-emergent adverse events by concizumab dose level during the main + extension parts of explorer4 (HAwI, HBwI) and explorer5 (HA); safety analysis set.

	explorer4								explorer5							
	0.15 mg/kg (N=25)		0.20 mg/kg (N=13)		0.25 mg/kg (N=4)		Total (N=25)		0.15 mg/kg (N=36)		0.20 mg/kg (N=21)		0.25 mg/kg (N=11)		Total (N=36)	
	n (%)	E [R]	n (%)	E [R]	n (%)	E [R]	n (%)	E [R]	E [R]	E [R]	n (%)	E [R]	n (%)	E [R]	n (%)	E [R]
Exposure time, including follow-up years	33.4		9.4		2.5		45.3		42.8		15.3		13.9		71.9	
All AEs	21 (84.0)	104 [3.1]	9 (69.2)	24 [2.5]	2 (50.0)	3 [1.2]	22 (88.0)	131 [2.9]	28 (77.8)	201 [4.7]	14 (66.7)	53 [3.5]	9 (81.8)	44 [3.2]	33 (91.7)	298 [4.1]
Serious AEs	4 (16.0)	8 [0.2]	1 (7.7)	1 [0.1]	0		5 (20.0)	9 [0.2]	2 (5.6)	2 [0.0]	1 (4.8)	1 [0.1]	2 (18.2)	2 [0.1]	5 (13.9)	5 [0.1]
Severe	2 (8.0)	4 [0.1]	0		0		2 (8.0)	4 [0.1]	1 (2.8)	1 [0.0]	1 (4.8)	1 [0.1]	2 (18.2)	2 [0.1]	4 (11.1)	4 [0.1]
Fatal	0		0		0		0		0		0		0		0	
AEs leading to withdrawal	0		0		0		0		0		0		0		0	
AESI (thromboembolic events)*	0		0		0		0		0		0		0		0	
AEs requiring additional data collection*																
Injection site reaction	6 (24.0)	16 [0.5]	1 (7.7)	3 [0.3]	0		6 (24.0)	19 [0.4]	14 (38.9)	28 [0.7]	1 (4.8)	1 [0.1]	1 (9.1)	1 [0.1]	15 (41.7)	30 [0.4]
Hypersensitivity type reaction	0		0		0		0		1 (2.8)	3 [0.1]	0		0		1 (2.8)	3 [0.0]
Medication error	1 (4.0)	1 [0.0]	0		0		1 (4.0)	1 [0.0]	0		0		0		0	

Patients and events presented with actual dose level at time of event when on treatment and last dose level afterwards.
*As reported by the investigator. %, percentage of patients with adverse event. AE, adverse event; E, number of adverse events; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; R, rate calculated as the number of adverse events per patient-years of exposure.