Efficacy, safety and surgical management with concizumab prophylaxis in three young patients affected by severe hemophilia with inhibitors

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ABSTRACT

Background: concizumab is an anti-tissue factor inhibitor monoclonal antibody designed as a once-daily subcutaneous prophylactic treatment for all hemophilia patients. The efficacy and safety of concizumab have been documented in the Explorer research program.

Objectives: we describe the management and clinical outcomes of 3 subjects treated with concizumab in the phase 3 Explorer 7 trial, in which patients with hemophilia A/B with inhibitors (HAPwI/HBPwI) were enrolled.

Methods: in 3 subjects (1 HAPwI and 2 HBPwI) followed in our Centre and enrolled in Explorer 7 trial the following data were collected: diagnosis, age at switch to concizumab, pre-switch antihemorrhagic treatment, venous access, joint involvement, bleeding events in the 6 months before switch, comorbidity, medications, quality of life (QoL), physical activity, date of switch and following bleeding events, treatment with recombinant activated factor VII (rFVIIa), surgery, QoL, physical activity.

Results: during the 5 years following the switch to concizumab all the patients had a drastic reduction in bleeding events and therefore of treatment with rFVIIa. A significant improvement in QoL, both in relation to pain reduction, movement ability and autonomy from caregivers, was achieved. No side effects were observed, and the management of 1 major and 14 minor surgeries did not present any bleeding or thrombotic complications.

Conclusions: concizumab represents a unique opportunity for HBPwI, but it may be of extreme value also for HAPwI. In our cases concizumab demonstrates and confirms clinical efficacy, positive impact on QoL and safety even in surgical settings.

Key words: anti-TFPI, efficacy, hemophilia, inhibitors, safety, surgery.

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Introduction

The development of inhibitors is the most severe complication in hemophilia treatment, altering the patient's therapeutic landscape.[1-4] These neutralizing antibodies render standard factors concentrate ineffective, preventing patients from receiving long-term prophylaxis and leading to uncontrolled bleeding episodes with an accelerated progression of debilitating joint disease.[5,6] For patients with hemophilia B (HB), this complication is even more dangerous, as inhibitors can trigger life-threatening systemic anaphylaxis during treatment.[7,8] The unpredictable nature of bleeds often results in frequent hospitalizations and a significant decline in the patient's quality of life (QoL). Beyond the physical risks, inhibitors impose a massive socio-economic burden,[9] requiring treatment with bypassing agents (BPAs) such as recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrates (aPCC)[10-12] and rigorous immune tolerance induction (ITI) protocols.[13-16]

The treatment landscape has been revolutionized by the introduction of novel non-factor therapies, specifically addressing the prophylaxis gap in patients with hemophilia and inhibitors (HPwI).[17] The bispecific antibody emicizumab (Hemlibra, Chugai/Hoffman-La Roche, Basel, Switzerland) mimics the function of activated FVIII (FVIIIa), linking activated factor IX (FIXa) and FX to facilitate thrombin generation.[18] This new class of drug adds complexity to acute bleed management (BPAs may still be needed) and requires specialized monitoring, but several studies demonstrated its importance in patients with hemophilia A (HA) with and without inhibitors.[19,20] Different agents targeting different parts of the cascade clotting have been developed, offering even more options for hemophilia management.

Concizumab (NovoNordisk, Copenhagen, Denmark) is a humanized IgG4 monoclonal anti-tissue factor pathway inhibitor (TFPI) antibody. At variance with emicizumab, it represents an alternative therapy also for HB with and without inhibitors.[21,22] It is administered daily and subcutaneously with a prefilled pen injector.

TFPI acts as a natural inhibitor of the initiation phase of coagulation, primarily by inhibiting activated FX (FXa) and the Tissue Factor/Factor VIIa (TF/FVIIa) complex. By binding to and inhibiting TFPI, concizumab removes this brake, allowing the extrinsic pathway to proceed further and produce more FXa, resulting in increased thrombin generation.[23,24]

The efficacy and safety of concizumab in HA or HB, with or without inhibitors, were documented in the Explorer research program.[24-27]

The Explorer7 trial was a multinational, multicenter, open-label, randomized trial that investigated the safety and efficacy of concizumab for routine prophylaxis in 133 HAPwI or HBPwI, aged 12 and older, who have been prescribed, or need treatment with BPAs.[25,26] The trial was comprised of 4 arms, two randomized arms and two nonrandomized arms: in arms 1 and 2, 52 patients (27 HAPwI, and 25 HBPwI), previously treated on-demand, were randomized 1:2 to no prophylaxis (arm 1: on demand treatment with BPAs) or concizumab prophylaxis (arm 2), with stratification by hemophilia type (HAPwI, HBPwI) and prior 24-week bleeding rate (<9 or ≥9); in arms 3 and 4, 81 additional patients (53 HAPwI and 28 HBPwI) were treated with concizumab prophylaxis. Treatment with concizumab included a loading dose of 1 mg/kg by subcutaneous injection on the first day and a daily dose of 0.2 mg/kg by subcutaneous injection starting on the second day. The dose was individualized to 0.25 mg/kg or 0.15 mg/kg if concizumab plasma concentration measured once after 4 weeks of treatment was <200 ng/mL or >4000 /mL, respectively, the therapeutic dose being in the range of 200-4000 ng/mL.

Here, we describe the management and clinical outcomes of 3 patients with hemophilia and inhibitors treated with concizumab in the context of Explorer 7 study.

Methods

The following data were collected for each patient: diagnosis, age at switch to concizumab, pre-switch antihemorrhagic treatment, venous access, joint involvement, bleeding events in the 24 weeks before switch, comorbidity, medications, quality of life (QoL), physical activity, date of switch and following bleeding events, treatment with rFVIIa, surgery, QoL, physical activity (Table 1).

Case report #1

Previous history

The patient is an 18-year-old male with severe HA (baseline FVIII levels <1%) with *F8* IVS-22 as pathogenic mutation. At the age of 19 months, after 4 infusions of octocog alfa for acute bleeding episodes, he developed high-titer inhibitor (90 BU/mL). He was switched to the BPA rFVIIa on demand and from March 2010 to March 2013 he underwent the first unsuccessful attempt of ITI with octocog alfa (200 U/kg/d). In October 2015, a second attempt with a lower dose (100 U/kg/d) of moroctocog alfa was undertaken but, due to a significant increase in inhibitor titer (historical peak 1390 BU/mL), in March 2016 ITI was discontinued. To ensure valid venous access, an arteriovenous fistula had been packaged before the first ITI. Since March 2017, because of the high frequency of muscle and joint bleeding poorly responsive to rFVIIa, he was put on prophylaxis with aPCC every other day with reduced advantage. In December 2017, at the age of 10, meeting eligibility criteria to participate to the phase 3, multicenter, nonrandomized, open-label HAVEN 2 study to investigate emicizumab prophylaxis safety and efficacy in HAPwI younger than 12 years of age,[28] he started the treatment. Unfortunately, 5 weeks after the start of emicizumab prophylaxis, he developed a neutralizing anti-drug antibody (ADA), with resumption of bleeding and subsequent discontinuation of emicizumab.[29] Then, a prophylaxis with aPCC (85 U/kg every 48 hours) was resumed. With the latter therapy, in the 6 months before switching to concizumab he had 6 bleeds at the following sites: left knee (2), right ankle (1), right elbow (1), 2 muscle hematomas, including one in his forearm and associated with pseudo-compartmental syndrome.

Each individual bleed was treated on average with 3 boluses of aPCC (85 U/kg) for a total of 72,000 U in addition to prophylaxis, with a total requirement of 430,000 U of aPCC and 108 intravenous infusions.

Clinical status at switching to concizumab

The patient showed chronic arthropathy of the left knee and right elbow. He had no comorbidities and was taking ibuprofen 400 mg as needed for joint pain.

The QoL was poor, the boy had severe limitations in daily activities, he was forced to use a wheelchair to move and was totally dependent on the caregiver (mother). The only physical activity he did was home physiotherapy.

Switch to concizumab and outcome

On 16 February 2021, at the age of 13 years, the patient was enrolled in the Explorer 7 trial in arm 4.

The dosage of concizumab remained unchanged as the circulating level at 4 weeks after the start of treatment was in the therapeutic range (1110 ng/mL; normal value: 200-4000 ng/mL).

Over 5 years from the switch the patient had 5 post-traumatic bleedings: 2 left knee hematomas, 1 right elbow joint bleeding, 1 left pretibial hematoma, 1 left knee joint bleeding. All bleeds were treated with rFVIIa (1-3 boluses 90 µg/kg). The only other treatments with rFVIIa were 3 single bolus 90 µg/kg for physical activity prophylaxis and a perioperative prophylaxis for major surgery. In October 2023 the patient underwent surgical closure of the arteriovenous fistula, which was no longer necessary and was creating a steal syndrome. Concizumab was discontinued 4 days prior to surgery. Perioperative antihemorrhagic prophylaxis included the following treatment: 2 boluses of 90 µg/kg rFVIIa every 2 hours at the beginning of surgery till wound suturing, followed by FVIIa 90 µg/kg every 4 hrs during the first 2 days, every 6 hrs on days 3-4, every 8 hrs on day 5, twice a day on days 6-7 and daily on days 8-14, then rFVIIa was discontinued.

Adjunctive intravenous tranexamic acid (TA) 1 g every 8 hours for 3 days was administered. The surgery required hos-

pitalization for 5 days. There were no bleeding or thrombotic complications, and on the day following discontinuation of rFVIIa, concizumab prophylaxis was resumed. Subsequently the patient underwent 3 hyaluronic acid injections at the left knee with concizumab prophylaxis only without bleeding complications.

The boy's QoL has profoundly improved, with a reduction in pain, autonomy of movement, the ability to carry out daily activities with peers and the acquisition of autonomy from the caregiver. A progressive increase in physical and recreational activity was possible, with the current practice of cycling, gym, soccer goalkeeper.

Table 1. Main characteristics of the patients treated with concizumab.

	Case #1	Case #2	Case #3
Diagnosis	Severe hemophilia A with inhibitors (*F8* IVS-22)	Severe hemophilia B with inhibitors (*F9* p.Arg252Stop)	Severe hemophilia B with inhibitors (*F9* large deletion – 814kb) Anaphylactic shock to rFIX
Age at switch	13	28	17
Pre-switch therapies	2 ITIs, rFVIIa OD, aPCC prophylaxis, emicizumab (HAVEN 2 study), aPCC prophylaxis (85 U/kg every 48 hours)	1 ITI, aPCC or rFVIIa OD, aPCC prophylaxis (75 U/kg every 72 hours) + rFVIIa (270 µg/kg) 22-23 days/month	rFVIIa OD
Venous access	Arteriovenous fistula (packaged for ITI)	No	No
Joint status	Arthropathy of the left knee and right elbow	Right knee arthroprosthesis, elbow arthropathy	Arthropathy of the right ankle and right elbow
Bleeding events in 6 months pre-switch	6 (2 left knee joint bleeding, 1 right ankle, 1 right elbow, 2 muscle hematomas, one of which associated with pseudo-compartmental syndrome)	≥1 joint bleeding/week at the right or left elbow	7 (1 gluteal hematoma, 1 left iliopsoas muscle hematoma, 3 right foot hematoma, 1 right ankle joint bleed, 1 at the elbow dx)
Antihemorrhagic therapy in 6 months pre-switch	aPCC: 430000 U	aPCC: 300000 UrFVIIa: 2000 mg	rFVIIa: 1184 mg
Comorbidities	No	No	Allergic rhinitis and conjunctivitis
Medications	Ibuprofen 400 mg OD	Eterocoxib 90 mg OD	Eterocoxib 90 mg 10 days/month + Nicetyl 500 mg 15 days/month. Antihistamines as required
Quality of life	Severe limitations in daily activities, use of wheelchair, caregiver dependence	Severe limitations in daily activities, pain	Limitations in daily activities, difficulty walking for long stretches, caregiver dependence
Activities	Home physiotherapy	Sedentary lifestyle	Physiotherapy twice weekly
Switch date	February 16, 2021	February 15, 2021	April 07, 2021
Bleeding events during 5-years follow-up	5 post-traumatic: 2 left knee hematomas, 1 right elbow joint bleeding, 1 left pretibial hematoma, 1 left knee joint bleeding	3: 1 post vaccination hematoma, 1 right elbow joint bleeding, 1 left elbow joint bleeding	2 post-traumatic right elbow joint bleeding
Treatments with rFVIIa	5 bleeds (1-3 boluses 90 µg/kg) + 3 single bolus 90µg/kg for physical activity prophylaxis + 1 perioperative prophylaxis for major surgery	Active chronic synovitis at the elbows3 bleeds (1-3 boluses 90µg/kg) + 11 boluses of prophylaxis (1 for 1 tooth extraction)	2 bleeds (1 bolus 90 µg/kg + 3 boluses 90 µg/kg)
Surgeries	Surgical closure arteriovenous fistula + 3 hyaluronic acid injections at the left knee	2 chemical synoviorthesis at the left elbow, 3 tooth extractions + dental treatments + 1 corticosteroid infiltration at the left elbow	Dental treatments: treatment of 3 dental caries + 2 scaling
Quality of life	Pain reduction, autonomy of movement, daily activities with peers, autonomy from the caregiver	Pain reduction, autonomy of movement, he moved to live in another city, started working and traveling	Autonomy of movement, daily activities with peers, autonomy from the caregiver
Activities	Progressive increase in physical and recreational activities: cycling, gym, soccer goalkeeper	Active life, gym or pool 3 times/week	Active life, gym 2- 3 times/week

rFVIIa, recombinant activated factor VII; ITI, immune tolerance induction; aPCC, activated prothrombin complex concentrates; OD, on demand.

Case report #2

Previous history

The patient is a 33-year-old male with severe HB (baseline FIX levels <1%) with *F9* p.Arg252Stop as pathogenic mutation. At the age of 2 years, after 22 infusions of nonacog alfa for acute bleeding episodes, he developed high-titer inhibitor (11 BU/mL). The historical inhibitor peak was 86 BU/mL. He was switched to the BPA aPCC on demand until age 15, when he started treatment with rFVIIa on demand to reduce the inhibitor titer and attempt an ITI. After 6 months, with 7 BU/mL inhibitor titer, he underwent an unsuccessful 30-month ITI with nonacog alfa (80 U/kg/d). He resumed treatment first on demand, then on prophylaxis with aPCC (75 U/kg every 72 hours). From June 2019 to December 2020, he was switched to prophylaxis with rFVIIa, subsequently, because of the high frequency of joint bleeding, he returned to prophylaxis with aPCC (75 U/kg every 72 hours) with reduced benefit and need for association with rFVIIa (270 µg/kg) 22-23 days/month to treat bleeds. In the 6 months before switching to concizumab he had ≥1 joint bleeding/week at the right or left elbow. Overall, the patient was treated with 2000 mg of rFVIIa in addition to 300,000 U of aPCC for prophylaxis.

Clinical status at switching to concizumab

The patient showed chronic arthropathy with synovitis of the elbows and right knee arthroprosthesis had been placed at age 23 years.

He had no comorbidities and was taking eterocoxib 90 mg as needed for pain from arthropathy. Regarding QoL, he had severe limitations in daily activities due to multidistrict pain with an extremely sedentary lifestyle.

Switch to concizumab and outcome

On 15 February 2021, at the age of 28 years, the patient was enrolled in the Explorer 7 trial in arm 4.

The dosage of concizumab remained unchanged as the circulating level at 4 weeks after the start of treatment was in the therapeutic range (328 ng/mL; normal value: 200-4000 ng/mL).

Over 5 years from the switch the patient had 3 post-traumatic bleedings: 1 hematoma of the left arm from anti-COVID-19 vaccine, 1 right elbow joint bleeding, 1 left elbow joint bleeding. All bleeds were treated with rFVIIa (1-3 boluses 90 µg/kg), additional 11 single boluses of rFVIIa 90 µg/kg were infused prophylactically into active chronic synovitis of both elbows and right knee. The only other treatment with rFVIIa was a single bolus 90 µg/kg for antihemorrhagic prophylaxis pre-extraction of tooth VIII molar. Two additional tooth extractions and dental treatments were carried out with concizumab prophylaxis only and mouth wash of TA. Likewise, the patient underwent 2 chemical synoviorthesis with rifampicin at the left elbow and 1 corticosteroid infiltration at the same site with only concizumab coverage without bleeding complications.

The impact on QoL improvement was significant, with a reduction in pain, autonomy of movement so much so that the patient moved to live in another city, started working and traveling. An active life has become possible, with the current practice of gym or pool 3 times/week.

Case report #3

Previous history

The patient is a 22-year-old male with severe HB (baseline FIX levels <1%) with *F9* large deletion (–814 kb) as pathogenic mutation and familiarity for high titer inhibitor. Due to the high risk of inhibitor development, the first bleeds (multidistrict muscle and subcutaneous hematomas, epistaxis) were managed with antifibrinolytics and rest. At the age of 5 years, after 4 infusions of nonacog alfa for extensive thigh hematoma, he developed low-titer inhibitor (1.4 BU/mL). After three months, on further infusion of nonacog alfa for shoulder joint bleeding, an anaphylactic shock occurred. Since then, he has always been treated with rFVIIa on demand. The FIX inhibitor peak was 1.7 BU/mL. No desensitization has been attempted, nor ITI has been performed.

Clinical status at switching to concizumab

In the 6 months before switching to concizumab he had 7 bleeds at the following sites: 1 gluteal hematoma, 1 left iliopsoas muscle hematoma, 3 right foot hematoma, 1 right ankle joint bleed, 1 right elbow joint bleeding, requiring a total of 148 infusions of rFVIIa 90 mg/kg equal to a total of 1184 mg.

He had chronic arthropathy of the right ankle and right elbow.

As a comorbidity he presented allergic rhinitis and conjunctivitis, for which he took antihistamines as required. He was also being treated with eterocoxib 90mg 10 days/month and Nicetyl 500mg 15 days/month for pain from arthropathy.

Regarding QoL, he had some limitations in daily activities, with difficulty walking for long stretches, and was dependent on the caregiver (mother) for the administration of antihemorrhagic therapy. The only physical activity he did was physiotherapy twice weekly.

Switch to concizumab and outcome

On 7 April 2021, at the age of 17 years, the patient was enrolled in the Explorer 7 trial in arm 4.

The dosage of concizumab remained unchanged as the circulating level at 4 weeks after the start of treatment was in the therapeutic range (524 ng/mL; normal value: 200-4000 ng/mL). Over 5 years from the switch the patient had 2 post-traumatic right elbow joint bleeding, both treated with rFVIIa 90 µg/kg (1 bolus at first bleeding and 3 boluses at second bleeding). The patient underwent treatment of 3 dental caries and 2 scaling with only concizumab coverage without bleeding complications.

The impact on QoL improvement was significant, with the acquisition of autonomy of movement, ability to carry out daily activities with peers and acquisition of autonomy from the caregiver. An active life has become possible, with the current practice of gym 2-3 times/week.

Discussion

Concizumab represents a novel, subcutaneous treatment option in HPwI that can potentially improve long-term outcomes. Results from the Explorer 7 study confirmed superiority of concizumab prophylaxis over no prophylaxis in reducing the annual-

ized bleeding rates (ABR) in HAPwI and HBPwI. Using a negative binomial model, a ratio of the ABR was estimated to 0.14 ($p<0.001$) corresponding to a reduction in ABR of 86% for HPwI on prophylaxis *versus* those on-demand treatment. The estimated mean ABR was 1.7 for HPwI on Concizumab prophylaxis and 11.8 for HPwI on no prophylaxis. Longer-term (≥1 year) efficacy and safety results of concizumab prophylaxis for HAPwI/HBPwI were consistent with the 32 and 56-week cut-off results in Explorer 7.[25,26] Concizumab and free TFPI concentration remained stable over time. Our 3 patients started prophylaxis with concizumab in 2021 and at 5 years apart presented only 5, 3 and 2 post-traumatic bleeding, respectively. A significant reduction in the need for BPAs treatments was consequential, such as the important impact on QoL. With protection from bleeding, all three experienced a reduction in pain, also demonstrated by a clear decrease in need for anti-inflammatories and painkillers drugs, as well as by a progressive improvement in movement, until achieving autonomy. This extraordinary result was particularly evident in the first patient, who needed a wheelchair to move around before switching to concizumab and then resumed walking. A progressive increase in physical and recreational activities was then inevitable, with the transition from a sedentary lifestyle, in which only physiotherapy was permitted, to the practice of different sports (pool, cycling, gym, soccer goalkeeper), allowing for normal daily activities with peers. All this has led to an unimaginable improvement in the QoL of the 3 patients.

Overall results of Explorer 7 clearly show that HPwI on prophylaxis with concizumab had better QoL compared to those treated on demand.[25,26] Furthermore, 93% of enrolled patients preferred concizumab to their previous treatment, based on the answers provided by the patients the main reasons were *fewer bleeds*, *require less time*, and *less painful to inject*.[30] Therefore, this preference is certainly related to the efficacy of the drug, but also to the route of administration of the drug and its simplicity and handling by the prefilled pen-injector.[31] These last two characteristics allowed the two young patients (cases 1 and 3) to become independent from their caregivers, with a further positive impact on their QoL.

Regarding the safety of concizumab, no significant critical issues have emerged in Explorer 7 study. The most common adverse reactions were injection site reactions (18%) and urticaria (6%). A serious adverse thromboembolic event (renal infarct) occurred in a HBPwI with multiple risk factors for thromboembolism (unknown renal infarct prior to trial entry, obesity due to Prader Willi Syndrome and treatment with rFVIIa for 3 days up to event). The Explorer 7 study did experience a temporary pause, then the trial resumed with a lower dose and stricter monitoring, and no other thromboembolic events were reported. Finally, no ADAs with neutralizing effect on concizumab were detected that impacted the drug's efficacy. Therefore, concizumab shows a significant safety profile and none of our patients had experienced adverse reactions or even injection site reactions.

The safety profile of concizumab is also emerging in the management of surgery, although experience is still limited. During Explorer 7 trial minor surgical procedures (defined as any invasive operative procedure were only the skin, mucous membranes or superficial connective tissue is manipulated) were permitted, and their management was at the investigator's discretion. Planned major surgery was not permitted, and for any cases of acute major surgeries, a concizumab pause was recommended at least 4 days prior to procedure to safely manage the higher bleeding risk with traditional BPAs. Concizumab therapy could be resumed 10-14 days after surgery on the same maintenance dose without a new loading dose. Perioperative topical use of antifibrinolytics was instead allowed. During Explorer 7 trial, at 56-week cut-off, 11 patients underwent a surgical procedure, of these 7 HAPwI and 4 HBPwI.[32] In total, 14 surgical procedures were performed, including 3 major surgeries. Dental procedures were the most frequent (7/14) and mild or moderate surgical-related bleeding episodes have occurred not infrequently, the high risk of mucosal bleeding in HPwI is in fact known. The median duration of minor surgery-related bleeding was 2 days, and the mean number of injections required to treat them was 1.7.[33] One severe bleed occurred linked to acute major surgery for a femoral neck fracture. Postoperative bleeding was successfully treated with rFVIIa and without thrombotic complications. The management of surgery in HPwI is notoriously more complicated and concizumab appears to have a safety profile, which is also demonstrated in our experience. A total of 15 surgical procedures were performed in our 3 patients, of these 14 were minor surgeries, consisting of 8 dental procedures and 6 intra-articular infiltrations. All procedures were managed with concizumab only, except extraction of an included molar tooth VIII for which an administration of a rFVIIa bolus prior to surgery was done. The management of the 3 tooth extractions included the use of TA (0.5 g every 8 hours for 7 days) as mouth wash. No bleeding complications occurred. Even in the management of the only major surgery consisting of arteriovenous fistula closure, no hemorrhagic or thrombotic complications were recorded, with discontinuation of concizumab and perioperative prophylaxis with rFVIIa, according to a protocol developed at our Center.

Conclusions

Concizumab therefore represents an important therapeutic option for antihemorrhagic prophylaxis in hemophilia patients, particularly in those with HB and inhibitors, with significant protection against bleeding. The short half-life makes surgery manageable with usual BPA concentrates with no significant safety signals reported in this setting.

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