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REVIEW

Concizumab as a Subcutaneous Prophylactic Treatment Option for Patients with Hemophilia A or B: A Review of the Evidence and Patient's Perspectives

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Abstract: Concizumab is a monoclonal, humanized IgG4 antibody specific for the Kunitz-2 domain of Tissue Factor Pathway Inhibitor (TFPI). Preclinical studies in vitro or on animal models and in vivo have demonstrated the ability of concizumab to restore thrombin generation, promoting the establishment of a procoagulant action; all these results were subsequently confirmed in the studies of EXPLORER program. Concizumab may represent a new opportunity for the treatment of persons with hemophilia, so there is much anticipation for the results of the ongoing trials still. This review retraces all the studies on concizumab published to date, with a brief discussion about the patient' perspectives.

Keywords: hemophilia, concizumab, anti-TFPI antibodies, new hemophilia treatments

Introduction

Hemophilia is a rare hereditary, X-linked, hemorrhagic disorder characterized by deficiency of coagulation factor VIII (hemophilia A) or IX (hemophilia B). A typical expression of this disease is spontaneous or traumatic bleeding which can cause the patient severe disability and, in the worst scenario, death. Prophylaxis with factor concentrates is started from an early age in children with severe or moderate hemophilia to minimize this hemorrhagic risk.

Despite the great efforts of clinical research, until recently there were no treatments other than replacement ones, but today a bispecific monoclonal antibody, emicizumab, is available to clinicians for the subcutaneous treatment of hemophilia A, while other subcutaneous drugs for the treatment of both, hemophilia A and B, are now in experimental phase, such as fitusiran, an antithrombin inhibitor, and the anti-TFPI (Tissue Factor Pathway Inhibitor) antibodies, as marstacimab or concizumab.

The long history of concizumab starts from afar, when it was still called *mab2021*, in fact the first report published by Petersen[1] that highlighted the hemostatic properties of this anti-TFPI antibody dates to 2012.

The idea that this antibody could be useful in the hemophilia treatment arises from the in vitro and animal model evaluation of its efficacy in blocking TFPI, thus allowing the tissue factor/activated factor VII (TF/FVIIa) complex to exert its action within the coagulation cascade, which ends with the clot formation. Butterfield et al[2] described the mechanism of action of different anti-TFPI antibodies in development, including concizumab, and the role these may play in the treatment of hemophilia. Here we retrace the concizumab history.

The purpose of this work is to review all reports on concizumab from in vitro studies to those dealing with its use in people with hemophilia A and B, and published from January 2012 to December 2021.

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Methods

A MEDLINE search using the key terms "concizumab", AND "mab2021" showed a total of 40 published reports. Two of them were immediately excluded, one because dealing with recombinant factor VIIa (rFVIIa) - the SMART study -, the other because "erratum". Among remaining 38 articles, thirteen deal exclusively with concizumab, four with TFPI inhibitors. New treatments for hemophilia are generically discussed in 18 reports, while the remaining 3 articles consider data regarding treatment costs, pharmacovigilance, and the impact of different treatments on joints.

Since the subject of the review is concizumab, only the 13 reports that deal with it specifically will be considered in this manuscript. In Table 1 the complete reviewed literature. Finally, a short section will discuss patients' perspectives regarding this new anti-TFPI antibody, still under study, compared to those of the available drugs.

Results

In 1998 Roberts et al[3] described the key role played by the complex TF/FVIIa in the coagulation cascade initiation. The authors highlighted in their in vitro model, and which mimics the in vivo condition, how this pathway initiates the coagulation by activating both factor IX (FIX) and factor X (FX). The result of these activations will be the conversion of prothrombin into thrombin, resulting in the fibrin clot formation. TFPI turns off this reaction, thus allowing proper hemostasis to be maintained. Structure, isoforms and mechanism of action of this serine protease inhibitor, have been comprehensively reported by Broze & Girard[4] and by Wood et al[5] The TFPI gene was cloned and completely characterized on 1988,[6] it measures approximately 90 Kb and is located on the long arm of chromosome 2 (q32), contains 10 exons and nine introns. Scientists have isolated several isoforms:[4,5] the TFPIα purified from plasma and conditioned media of HepG2 cells. It consists of an acidic aminoterminal (N-) region followed by three tandem Kunitz domains encoded by exons 4-6-9 and the intermediate peptides which are allocated among Kunitz domains encoded by exons 5 and 7, and by a carboxyterminal (C-) region; the TFPIβ initially discovered in mice, but also present in the ECV304 human cells of a bladder cancer presenting some endothelial characteristics; and the TFPIδ whose mRNA was found to be more expressed in the liver. In healthy people mean plasma TFPI concentration is about 70 ng/mL. TFPI circulates in plasma bound to lipoproteins, so its concentration depends on the low-density lipoproteins (LDL) amount, which can in turn be affected by the diet. Most plasma TFPI has a molecular weight between 34 and 41 kDa and is composed of 276 amino acids. In vitro models showed that TFPIα can be proteolytically degraded by a different proteinase, such as thrombin, plasmin, neutrophil elastase, or FXa if its molar quantity exceeds that of the TFPIα itself. Plasma concentrations of TFPIα were also reduced in patients with factor V (FV) deficiency, protein S (PS) deficiency and presumably also in those with FVIII deficiency. TFPI turns off the coagulation cascade with an irreversible process that requires the presence of calcium, and which is enhanced by the action of protein S. The structure of TFPIα, the most present isoform in plasma, is illustrated in Figure 1.

Table 1 All Concizumab Papers Considered in This Review

Reference (n)	Authors	Year	Model	Phase (trial)
[10]	Hilden I et al.	2012	Animal (rabbits)	
[11]	Agersø H et al.	2014	Animal (monkeys)	
[12]	Hansen L et al.	2014	Animal (rats, rabbits)	
[13]	Lauritzen B & Hilden I	2019	Animal (rabbits)	
[14]	Lauritzen B et al.	2019	Animal (monkeys, rabbits)	
[15]	Chowdary P et al.	2015	Human	I (Explorer 1)
[16]	Chowdary P et al.	2018	Human	I (Explorer 1)
[17]	Waters EK et al.	2017	Human	2 (Explorer 2)
[18]	Eichler H et al.	2018	Human	3 (Explorer 3)
[19]	Shapiro AD et al.	2019	Human	2 (Explorer 4/5)
[20]	Shapiro AD et al.	2021	Human	2 (Explorer 4/5)
[21]	Yuan et al.	2019	Human/Animal (rats/rabbits)	
[22]	Kjalke M et al.	2021	In vitro	

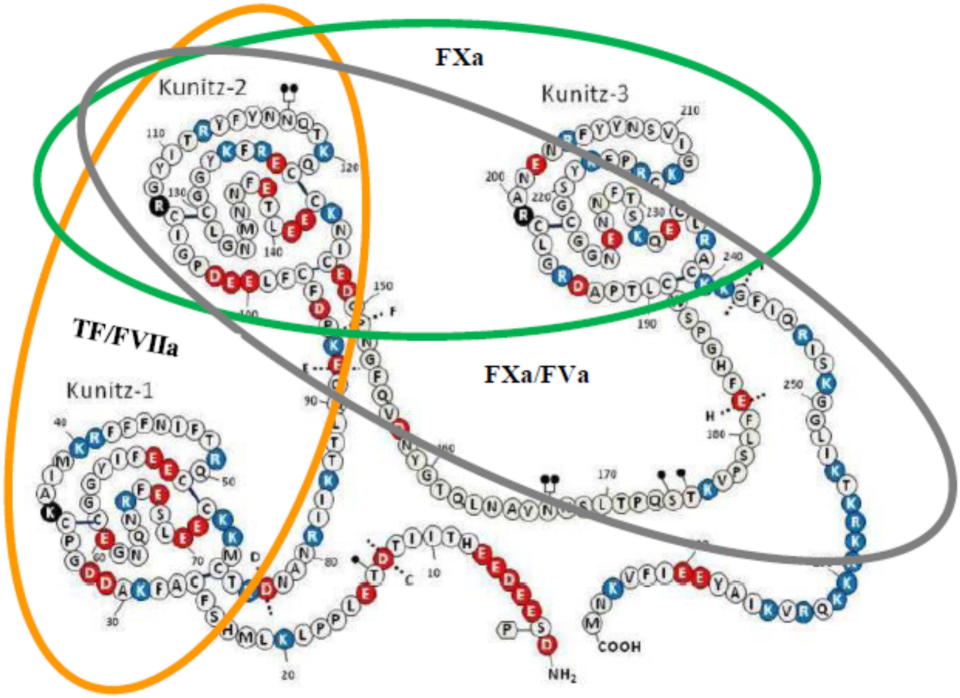

Figure 1 Structure of TFPIα.
Notes: The domains required for inhibition of FXa, and of TF/FVII and FXa/FVa complexes are enclosed in the green, Orange, and grey ovals, respectively. Republished with permission of Frontiers in Bioscience, from Tissue factor pathway inhibitor: structure-function, Broze GJ, Girard TJ, Volume 17, Edition 1, 2012; permission conveyed through Copyright Clearance Center, Inc.[4]

The TFPI activity takes place at the level of the Kunitz domains. The first domain inhibits the TF/FVIIa complex, the second one inhibits FXa, while the third is only involved in binding to lipoproteins and heparins, without any known inhibitory function. The C-terminal region seems to favor contemporary interaction of TFPI and FXa to the phospholipid surface, and it is also involved in the FXa inhibition. Some in vitro models have indeed shown that the TFPI molecules lacking from the C-terminal region have a reduced anti-Xa and anticoagulant effect. All these inhibitory actions of the TFPI, which consequently lead to a drastic reduction of thrombin generation, may help explain the excessive bleeding in patients with hemophilia. Therefore, inhibiting the action of TFPI can be a strategy to be used in new drugs, such as concizumab, for the treatment of this hemorrhagic disease. The mechanism of action of TFPI is reported in Figure 2.

Concizumab is a monoclonal, humanized IgG4 antibody specific for the Kunitz-2 domain. Preclinical studies in vitro or on animal models and in vivo have demonstrated the ability of concizumab to restore thrombin generation, promoting the establishment of a procoagulant action.[1,7–9]

Animal Models

In 2012 Hilden et al[10] published the results of four independent studies performed in rabbit models after induction of hemophilia with a FVIII antibody (Ab). The first two were a dose-response studies in which the rabbits, induced cuticle bleeding, were randomized to receive *mab2021* intravenously or isotype control Ab. In the third study hemophilic rabbits, induced cuticle bleeding, were instead randomized to receive rFVIIa, *mab2021*, or isotype control Ab. The last study tested the efficacy of *mab2021* administered subcutaneously. In all studies use of *mab2021* reduced the blood loss, shortening the bleeding time. Very encouraging for the future of this new monoclonal antibody was its efficacy highlighted also in case of subcutaneous administration.

Two years later Agersø et al[11] published an interesting pharmacokinetic (PK) report in which two different studies performed in Cynomolgus Monkeys were described. In the first study twelve animals were divided in five different groups. The first three groups (2 monkeys/group) were included in a multiple dose PK study with escalating dose levels

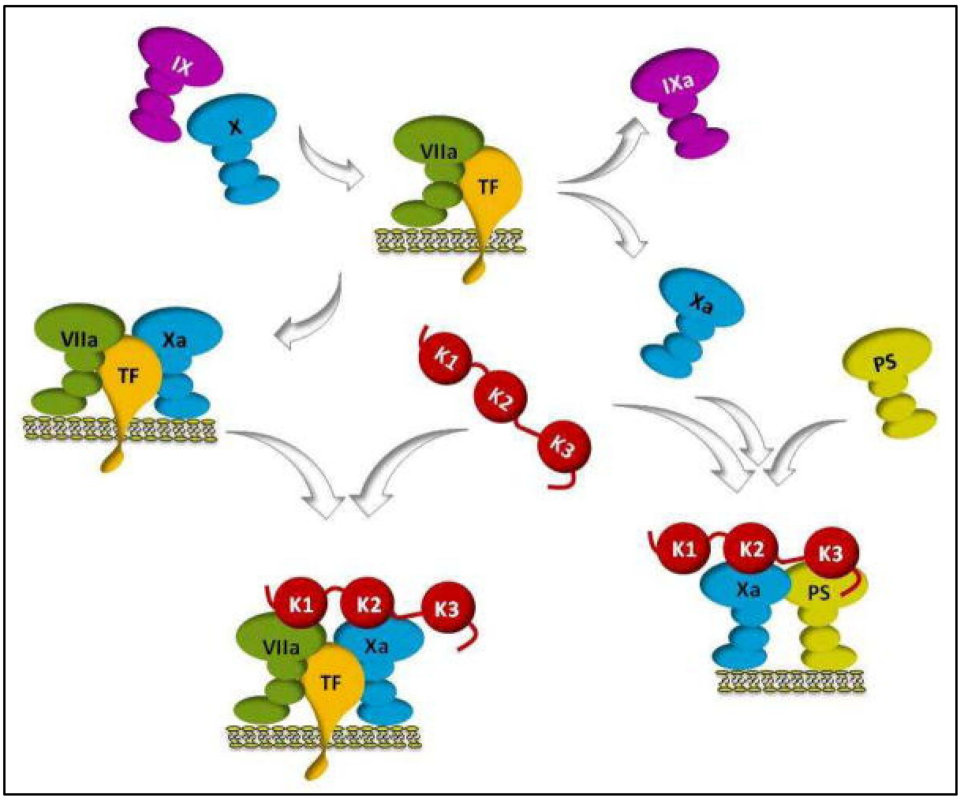

Figure 2 Mechanism of action of TFPI.
Notes: Republished with permission of *Frontiers in Bioscience*, from Tissue factor pathway inhibitor: structure-function, Broze GJ, Girard TJ, Volume 17, Edition 1, 2012; permission conveyed through Copyright Clearance Center, Inc.[4]

administered every two weeks. For each group, blood samples were subsequently collected pre-dose and at different times. The remaining two groups were included in a single dose PK-study in which 20 mg/kg of concizumab were administered to monkeys intravenously or subcutaneously. Blood samples were subsequently collected pre-dose and at fourteen different times after drug administration. The second study was a thirteen-week toxicity study performed in fifty animals divided into four different groups based on the dose of administered drug and route of administration. Blood samples were after collected at different times for each group. These studies showed that the PK of concizumab was characterized by a high bioavailability (93%) after subcutaneous administration, with a clearance of 0.14 mL/h/kg, and reaching steady state after one week, slower in case of daily drug administration due to clearance-mediated target saturation. The potential efficacy of concizumab administered subcutaneously highlighted in the hemophilic rabbits' study is therefore confirmed by these pharmacokinetic results.

Similar data were obtained in the same year by Hansen et al[12] In their study the role of concizumab in neutralizing the TFPI inhibition in human endothelial cell-like immortalized cell line EA. hy926WT, derived from umbilical vein cells, was proven, while the PK profile was studied in both rats and rabbits.

Lauritzen & Hilden in their letter to editor, recently published,[13] described three independent studies performed on hemophilic rabbits. These studies confirmed previous data: escalating doses of concizumab administered within five minutes from cuticle bleeding induction are equally effective to reduce the ongoing bleeds, but concizumab resulted less effective than rFVIIa if administered 15–30 minutes after bleeding induction. These data suggest that the use of rFVIIa is more suitable for the treatment of acute bleeding, while the use of concizumab is more appropriate for prophylaxis.

Another report always published by Lauritzen et al[14] explored the efficacy and the safety of concizumab and rFVIIa when simultaneously administered. Three different studies were described. The first was an in vitro study in which the

human blood was taken from healthy donors and the platelet rich plasma (PRP) was subsequently prepared by centrifuging the whole blood. Hemophilia was induced ex vivo by adding a polyclonal sheep FVIII-antibody. Thrombin Generation Test (TGT) was then performed for PRP after adding concizumab, rFVIIa or a combination of concizumab and rFVIIa in equal parts. Both, concizumab and rFVIIa, increased thrombin peak in hemophilia A-like blood, while the combination of these two drugs caused a synergistic effect. Results subsequently confirmed with the thromboelastography.

In the second study the efficacy of concizumab, rFVIIa and a combination of concizumab/rFVIIa was tested in different groups of hemophilic rabbits after cuticle bleeding induction. The obtained data confirmed that both, concizumab and rFVIIa, were equally effective in reduce bleeds after cuticle bleeding induction, but the combination of these two drugs did not bring any additional effects and did not increase hemostatic efficacy.

The last study evaluated the safety of concizumab in a group of Cynomolgus Monkeys. Concizumab or vehicle control were daily administered to animals by subcutaneous injection for 28 days. A concizumab loading dose of 9.0 mg/kg was administered to monkeys for four days, followed by a dose of 1.0 mg/kg from day 5 to day 28. On day 28 the animals in the concizumab group also received three subsequent escalating doses of rFVIIa (0.25–0.5 – 1.0 mg/kg) two hours apart. Steady state of concizumab in plasma was reached after 27 days in all animals, except in one that had developed inhibitors against concizumab. No clinical adverse events nor thrombi during pathological examinations have been found. In conclusion concizumab in animal models resulted effective in reduce bleeding and safe.

The EXPLORER Trials

The Explorer 1[15,16] was a first trial in humans. In this study escalating single doses of concizumab (intravenously or subcutaneously) were administered to healthy volunteers and persons with hemophilia (PWH) A or B. The study was a Phase 1, multicenter, randomized, double blind, placebo controlled, single dose and dose escalation trial. The participants enrolled in this study were randomized 3:1 to receive a single dose of concizumab (3 subjects) or placebo (1 subject). Dosing was initiated in healthy volunteers and, subsequently, continued in PWH. The primary end point of the study was safety, assessed at well-defined intervals up to 43 days after concizumab administration.

Pharmacokinetics (PK) and pharmacodynamics (PD) were also assessed throughout the entire study. 52 participants were overall included in the Explorer 1 trial, 28 were healthy volunteers, while 24 were PWH (21 with hemophilia A and 3 with hemophilia B). Throughout the trial 76 adverse events (AEs) were reported, 75% of them were mild, but none was a serious event. 19 AEs occurred in the placebo group. No correlation among different doses of concizumab and the onset of adverse event was found. The PK of concizumab was found to be non-linear and similar between PWH and healthy subjects. The PD analyses showed that the plasma unbound TFPI profiles were inversely related to PK ones, in fact the unbound TFPI concentration in plasma decreased if the concizumab concentration increased and remained decreased for over 14 days post dose at the highest concizumab levels. 24 bleeds were reported in 14 PWH (5 placebo; 9 concizumab), while only one bleed occurred in a healthy volunteer given concizumab. Except one, no bleeds were recorded in the subjects presenting in plasma high concizumab levels and low unbound TFPI concentrations. Concluding data from this study therefore demonstrate that also in humans concizumab can be considered a safe drug both intravenously or subcutaneously, as already shown in animal models.

Like the previous study, the Explorer 2 trial had as end points the evaluation of safety, PK and PD of concizumab administered subcutaneously to healthy male subjects and PWH. Waters et al[17] investigated the role of concizumab in the thrombin generation, both in PWH and in healthy volunteers. A total of 22 participants were included in two different studies, 18 were hemophiliacs, while the remaining 4 were healthy males whose blood samples were obtained from the Explorer 2 trial. The thrombin generation, assessed by the thrombin generation assay (TGA), increased with concizumab after ex vivo spiking of hemophilia plasma and multiple subcutaneously doses in healthy subjects.

Another study on the safety of concizumab in PWH was the Explorer 3 trial.[18] This multicenter, phase 1b trial investigated five escalating dose cohorts, each cohort had eight hemophilia patients and was divided into two different blocks. The study was placebo controlled, then two arms of treatment were defined: the concizumab arm and the placebo one. The assessed end points were safety, PK and PD, and the subcutaneous immunogenicity of concizumab at different doses. Overall, 24 participants were enrolled in this trial, equally divided in three different concizumab dose groups

(0.25-0.5–0.8 mg/kg) subcutaneously administered every four days. In each cohort six patients received concizumab and two placebo. A total of 56 adverse events occurred in 19 patients were reported, 54 of them mild and the remaining two moderate. The number of AEs was not related to the concizumab dose increase. PK and PD obtained in this trial confirmed as described in the previous studies. 91 bleeds were described, 28 of them in five patients in placebo group. Almost all bleeds were mild, except for two severe episodes, one spontaneous hemarthrosis and one traumatic muscle bleeding, which occurred in the concizumab 0.5 mg/kg group and the placebo group, respectively.

Explorer 4 and Explorer 5 trials[19,20] were two different Phase 2 studies created to assess the efficacy and safety of subcutaneous concizumab administration in persons with hemophilia A or B (PWH-A or -B) with inhibitors (Explorer 4) and in severe PWH-A without inhibitors (Explorer 5), and to establish the optimal dose of concizumab for the subsequent Phase 3 studies. 36 PWH-A, 9 PWH-A with inhibitors and 8 PWH-B with inhibitors were enrolled in these studies and treated with concizumab 0.15 mg/kg, with potential dose escalation to 0.20 and 0.25 mg/kg in case of three spontaneous bleeds within twelve weeks of study drug treatment. The assessed PK/PD parameters confirmed the results of phase 1 trials. Estimated annual bleeding rate (ABR) was lower in patients with inhibitors than in those without (3.0 vs 5.9), and only two of seventeen inhibitor patients escalate the dose. All patients chose to participate to the extension phase of the trials. In these trials concizumab resulted safe and well tolerated, no severe event adverse or thromboembolic episodes were reported. Three patients in each study (Explorer 4 and Explorer 5) developed antibodies against the drug (ADA), without clinical manifestations. All three patients in the non-inhibitor trial developed a very low ADA titer (1.0–16.0 ng/mL), while the other three in the inhibitor trial presented a medium ADA titer (1.0–128.0 ng/mL) considering the assay sensitivity of 1.0 ng/mL. Neutralizing ADA in vitro were found only in one determination in two participants to Explorer 4 trial and in one of participants to Explorer 5 study. No changes in PK/PD or laboratory parameters, no increased bleeding, no adverse events were

reported in PWH developing ADA compared to patients without antibodies. These data support the daily use of concizumab as prophylactic treatment in all hemophilia subjects.

The Explorer program is still ongoing, and the results of the phase 3 trials are not yet published.

Other Studies

The remaining two published reports[21,22] analysed the pharmacokinetics and pharmacodynamics of concizumab. Yuan et al[21] created a system PK/PD model based on the different data of pharmacokinetics and pharmacodynamics of concizumab in humans,[15] rabbits[12] and monkeys.[11] This model may be useful to determine the correct dose regimen of concizumab for the hemophilia treatment. Kjlke et al[22] performed an interesting study in vitro and ex vivo aimed at evaluating the thrombin generation (TG) of concizumab alone or together with rFVIIa, activated prothrombin complex concentrate (aPCC) or recombinant FVIII (rFVIII). These drugs were added to plasma obtained from hemophilia A patients receiving concizumab, and subsequently analysed. In case of hemophilia B the TG was assessed only for concizumab alone or together with recombinant FIX (rFIX), after being added to the plasma of patients treated with concizumab. Similar as highlighted in the previous studies, concizumab was proven to increase the thrombin generation peak following a dose-dependent model. A combination of concizumab and rFVIIa, aPCC, rFVIII (or rFIX) caused an addictive effect, highlighted by the TG assay, but without a synergistic strong effect. This study showed also that 0.5 IU/mL of rFVIII (or rFIX) added to concizumab had given rise to a TG peak comparable to that obtained with 1.0 IU/mL of rFVIII (or rFIX) alone. Given these addictive effects, the use of concizumab in combination with other hemostatic agents should be carefully monitored and their dosage adjusted in order not to cause serious adverse events.

Patient's Perspectives

Over the years, the unmet needs of PWH have changed. Until the discovery of cryoprecipitate by Judith Pool[23] in 1965, the greatest need for these people with coagulation disorders was to have a drug available to stop acute bleeding, a cause of disability and in the worst cases of death.

The discovery of this anti-hemophilic factor triggered the subsequent development of plasma-derived coagulation factor concentrates. With the advent of these drugs, PWH's life expectancy increases, bleeding is better controlled, and the concept of prophylaxis begins to be instilled in clinicians.

In the 80–90s, the consequences of HIV and HCV transfusion-transmitted infections have led to an increasing need for safety in the drugs used for the PWH's treatment. In this period, drugs of recombinant origin were developed that respond to the need for viral safety. Over time, thanks to the availability of many drugs with slightly different characteristics, the clinician tries to give each patient the best therapy, effective, safe and free as much as possible of the risk of developing antibodies against FVIII or FIX. The concept of tailored therapy was born.

If efficacy in treating bleeding and safety in preventing the risk of viral infections and the development of inhibitors remain among the primary needs of PWHs, others are their requests that are becoming increasingly important in the management of hemophilia.

In 2017 von Mackensen et al[24] highlighted how the lower frequency of infusions ranks first among the unmet needs of PWH, while the improvement in their quality of life is mentioned in fifth place. The availability of the extended half-life FVIII and FIX concentrates have undoubtedly contributed to meeting these needs, but it is the advent of new non-substitutive drugs, administered subcutaneously, which will lead to an epochal change in the treatment of PWH. Parnes et al[25] analyzed the data from two phase 3[26,27] studies involving the bispecific antibody, emicizumab. In the Haven 3 trial ninety-five patients receiving the study drug completed the EmiPref survey, and 94% of them reported preferring emicizumab to their previous treatment while in the Haven 4 trial, all enrolled patients completed the EmiPref survey, with all reporting a preference for emicizumab over their prior treatment. Efficacy and ease of administration have allowed this drug to gain the preference of patients.

The thromboembolic risk, almost unknown to PWHs treated with factor concentrates, becomes of primary importance in the case of these new non-replacement therapies, especially in those that act on the coagulation system, reducing the levels of anticoagulant activity, compensating for the defect in procoagulant activity, and thus increasing the thrombin generation.[28,29] Concizumab falls into this category. In fact, the pivotal studies, Explorer 6, Explorer 7, and Explorer 8, have been temporarily stopped in March 2020 after non-fatal thrombosis occurred in three different participants. The studies were restarted a few months later, but with a new reduced dosing regimen of drug to mitigate the thromboembolic risk, as recently presented to the "15th Annual Congress European Association of Haemophilia and Allied Disorders (EAHAD)" by Chowdary et al[30] and Astermark et al[31] All three participants to clinical trials who experienced these adverse events had distinct thrombotic risk factors,[30] therefore maximum attention must be paid to concizumab use especially in subjects at greater risk of thromboembolic events, such as the elderly with underlying cardiovascular problems, or in case of association with other anti-hemorrhagic drugs.

Subcutaneous administration of these drugs has created great expectations especially for the treatment of younger hemophilia patients, but the exclusion of newborns (< 1 year-olds) from the pivotal studies, associated with the variability of the hemostatic system found in children of different ages, makes it difficult to define with certainty the use of these non-replacement therapies in this population of patients.[32]

Certainly, both patients and clinicians expect a lot from concizumab and the other subcutaneous drugs, available as emicizumab, or still in development, but long-term studies and registries are needed to give them a valid answer.

Conclusion

The development of new subcutaneous drugs has marked a milestone in the hemophilia treatment, changing the paradigm of patient's management.

A drug as emicizumab has in fact allowed PWH-A with inhibitors to lead a life like that of those who do not have these antibodies. A weekly, bi-weekly or even monthly prophylaxis regimen has reduced the use of bypassing agents and of long and not always effective immunotolerance induction (ITI) regimens. The reduction in bleeding that led to almost complete zeroing of ABR significantly improved the quality of life of these patients. Inhibitor appearance in PWH-B is very rare, but their treatment is very difficult, in fact, attempts to eradicate the antibodies by using FIX at high doses, as occurs during ITI, can cause the development of anaphylactic reactions, even severe, in over half of the patients treated. Therefore, these patients have only one therapy available, the use of rFVIIa, a drug with a very short half-life which requires very frequent infusions. The new subcutaneous drugs that can be used in PWH-AB, which act on the coagulation system by rebalancing it, such as concizumab and the other anti-TFPIs or the antithrombin inhibitor, fitusiran, can certainly represent a future therapeutic option also for patients with FIX deficiency.

In the case of patients who do not have inhibitors against FVIII or FIX, these subcutaneous drugs may represent an important turning point in initiating primary prophylaxis in children. In fact, the initiation of prophylaxis is now delayed mainly due to their difficult venous access. Of course, large studies and registries are needed to define the safety of these drugs in infants and newborns.

Safety is also a very important topic in adults, as several cases of thrombosis in humans have been reported, not detected in animal models, and which have also led to the temporary suspension of pivotal studies, this should suggest to clinicians the need for some attention in the future use of these new drugs.

After these due considerations, we can affirm that the preliminary data on concizumab, which emerged from the first studies, are encouraging, but the outcome of the ongoing trials is awaited to define with certainty advantages and limits of this drug.

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Disclosure

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