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Review Article
https://doi.org/10.63501/6h426j60

Concizumab: A Subcutaneous TFPI Inhibitor for Hemophilia A and B Prophylaxis

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ABSTRACT

Introduction: Hemophilia is a rare X-linked bleeding disorder caused by deficiencies in clotting factors VIII (Hemophilia A) or IX (Hemophilia B), leading to spontaneous joint bleeding and recurrent bleeding after trauma. The treatment of hemophilia includes IV factor replacement therapy. It is limited by high cost, inhibitor development, short half-life, and significant psychological and financial burden. Concizumab offers a convenient subcutaneous alternative that enhances thrombin generation and improves clot formation.

Objective: To assess the efficacy and safety of concizumab in hemophilia A and B (with or without inhibitors), as well as evaluate its performance against current therapeutic options in the modern treatment landscape.

Result: Concizumab is a monoclonal antibody that blocks the K2 domain of TFPI, preventing FXa inhibition and thereby restoring thrombin generation, thereby improving coagulation in patients with hemophilia. The phase 2 EXPLORER 4 and 5 trials showed that subcutaneous concizumab reduced bleeding rates in patients with hemophilia A and B, with or without inhibitors. The phase 3/3a EXPLORER 7 and 8 trials confirmed reduced spontaneous and traumatic bleeding, with improved safety following dose adjustments. EXPLORER 10 demonstrated similar benefits in children, with improved clotting activity and low rates of bleeding. Improvements in bleeding rates and convenience were also associated with emicizumab, fitusiran, gene therapy, and rFVIIa — in contrast to concizumzb. But their use was compromised by inhibitor development and thrombotic risk. The high cost, limited applicability across hemophilia subtypes, and uncertain long-term safety also restricted their use. These provided what was perceived as an unmet need for a safe, effective, and easy-to-use treatment, which prompted the development of concizumab.

Conclusion: A TFPI inhibitor, concizumab, has shown benefit in hemophilia trials and is being evaluated

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for long-term use. It complements other clotting therapies and may be beneficial in other bleeding disorders. For the most part, it is a safe and convenient non-factor treatment with broad possibilities.

KEYWORDS:*Concizumab, Hemophilia, Tissue Factor Pathway Inhibitor (TFPI), Monoclonal antibody, Non-Factor Therapy, Thrombin generation, Bleeding prophylaxis, Non-factor therapy*

INTRODUCTION:

Hemophilia is a rare X-linked bleeding disorder, characterized by a deficiency or absence of clotting factors leading to impaired clot formation. It is broadly classified into 2 types, A and B, deficiencies that are signified by deficiencies in Factor VIII and Factor IX, respectively. Males have a higher ratio of being affected as compared to females due to the X-linked nature of the disease. With a frequency of one in 5,000 live male births, hemophilia A (HA) is more common than hemophilia B (HB), which occurs one in 30,000 (1). Moreover, the severity of hemophilia is classified into 3 types based on the level of factor VIII or IX activity: mild (> 5%), moderate (1-5%), and severe (< 1%) (2). Patients usually present with spontaneous bleeding generally affecting the knee, elbow, and ankle joints (hemarthrosis) and recurrent bleeding related to trauma (3). Bleeding may also occur at other sites, such as mucous membranes and the central nervous system (CNS), as well as post-surgery (4).

Clot formation has 2 activation pathways: Intrinsic and Extrinsic. The extrinsic pathway is activated by endothelial damage, which exposes Tissue Factor (TF/Factor III) that binds with Factor VII to form a TF-Factor VII complex that activates Factor X. The intrinsic pathway, on the other hand, is classically thought to be activated by surface collagen exposure that cleaves Factor XII and initiates a cascade of events eventually leading to activation of Factor X via intermediates of Factor XI, IX, and VIII (5). However, recent understanding leans more toward a cell-based model of hemostasis. This model describes coagulation in three overlapping phases: initiation, amplification, and propagation on cell surfaces. In hemophilia, deficiencies of FVIII or FIX affect the propagation phase, reducing the thrombin burst, which is essential for stable clot formation (6). These phases collectively convert Factor II to IIa. Hence, the deficiency of Factor IX or VIII impairs the intrinsic pathway of clot formation (5).

The primary treatment for hemophilia is intravenous (IV) factor replacement therapy, which involves the administration of plasma-derived concentrates or recombinant factors VIII and IX(7). While it has significantly improved patients' lifespans, there are some setbacks, too. The major issue is the development of inhibitors with a 3-fold higher risk in HA than in HB. Age and race also significantly influence the risk factor(4). Additionally, these treatments are very costly, requiring long-term administration and multiple clinical visits, making them a financial burden for the family and thereby decreasing accessibility (8). Another major issue is the risk of transfusion-related infections, such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) (9), although this risk is now essentially eliminated in developed countries due to modern recombinant and virus-inactivated plasma-derived products, which use dedicated viral inactivation steps and rigorous screening (10). Moreover, due to the factors' short half-lives, continuous laboratory monitoring and frequent injections are required. IV administration is invasive and inconvenient, especially in young children (11). Long-term treatment also has a negative psychological impact on the patient, leading to episodes of anxiety and depression. Over time, the financial and emotional burden of the treatment can impair quality of life (8). While factor replacement therapy is a life-saving option, its invasive nature, high ongoing costs, and limited accessibility, particularly in low-resource settings, make it relatively cost-ineffective compared to newer agents; therefore, newer alternatives are an urgent requirement in hemophilia treatment (4).

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Concizumab is a newer, innovative approach to hemophilia management compared to traditional methods that replace the deficient clotting factor. Concizumab is a monoclonal IgG antibody specific for Tissue Factor Pathway Inhibitor (TFPI) that inhibits thrombin formation (12). It works by enhancing the ability to form clots by generating thrombin. Additionally, it is effective in both hemophilia A and B, with or without inhibitors, and is an excellent alternative for those who do not respond to standard factor replacement therapy (13). Subcutaneous administration, rather than IV, is a major advantage and improves patient outcomes, reduces healthcare burden, and enhances accessibility compared to factor replacement therapy. It is a less invasive approach and offers a more comfortable, flexible dosing schedule individualized based on patient weight, bleeding phenotype, and treatment response, making it a turning point in hemophilia treatment (3).

METHODOLOGY:

This narrative review evaluates published literature on Concizumab for the management of Hemophilia A and B. Electronic databases, including ClinicalTrials.gov, Google Scholar, and PubMed Central, were searched from database inception to March 31, 2025, with a subsequent update performed in August 2025. This update includes references published up to November 2025. Search terms included (Hemophilia OR Hemophilia A OR Hemophilia B) AND (Concizumab OR anti-TFPI antibody OR anti–tissue factor pathway inhibitor) AND (Monoclonal antibody OR mAb therapy) AND (TFPI inhibitor OR TFPI-targeted therapy). Only studies published in English were considered. Inclusion criteria comprised clinical trials (Phase I–III), observational studies, systematic reviews, meta-analyses, and pharmacokinetic/pharmacodynamic studies evaluating concizumab in Hemophilia A or B, with or without inhibitors. Reference lists of eligible articles and relevant conference abstracts were also screened to ensure comprehensive coverage. Exclusion criteria included duplicate records, non-English-language publications, editorials without primary data, and studies that did not directly address concizumab or TFPI-targeted therapy.

MECHANISM OF ACTION:

The strategies for treating hemophilia, both with inhibitors and without, focus on promoting adherence to therapy and improving a patient's condition. An area of interest is the silencing of the tissue factor pathway inhibitor (TFPI), a coagulation regulator (14). TFPI is an inhibitor of a serine protease that, by inhibiting activated factor Xa (FXa), acts to control thrombin generation at the site of blood clotting. This will prevent excessive levels of thrombin from being produced by inhibiting the tissue factor (TF)/activated factor VIIa (FVIIa) complex, in an FXa-dependent fashion, as well as the initiation of the activated FVa/FXa prothrombinase complex (15).

Both VIII and IX factors are not produced in sufficient quantities in hemophilia, resulting in very low levels of FXa. While the coagulation process starts normally, it is not amplified. An increase in thrombin was found to promote prothrombin aggregation and inhibit thrombin (14). TFPI also suppresses the Tanase complex, which is responsible for forming FXa, as well as the early pre-prothrombinase complex, which contains the activated cyclin-dependent protease FXa and FVa. This study aims to limit the amount of TFPI that is controllable, thereby achieving a stable coagulation system with reduced recurrence (3).

Concizumab hinders TFPI from blocking thrombin, thereby favoring factor X activation. A nonclinical study identified its ability to restore thrombin generation in patients with FVIII or FIX deficiency and characterized it as having high affinity for TFPI. The humanized monoclonal antibody concizumab specifically binds the Kunitz-2 (K2) domain of TFPI, which is the domain responsible for inhibiting activated FXa. By binding to TFPI-K2, concizumab prevents TFPI from inactivating FXa, thereby allowing FXa to continue driving thrombin

generation even in the absence of FVIII or FIX. Additionally, blocking TFPI at the K2 domain indirectly reduces TFPI's inhibition of the TF/FVIIa complex because TFPI requires FXa engagement through the K2 domain for full inhibition of TF-initiated(3,14). In preclinical trials with hemophilia patients, they experienced shorter bleeding duration and less total blood loss. In the Explorer trial involving concizumab, patients experienced no safety concerns and did not develop anti-drug neutralizing antibodies, which is a marker of safe use in hemophiliac patients (14). Mechanism of action of TFPI and concizumab is reported in Figure 1:

Concizumab, a monoclonal antibody administered subcutaneously, represents one of the most promising advancements in hemophilia treatment, offering numerous crucial advantages. Bioavailability is impressive at 93% after subcutaneous injection, eliminating the need for intravenous dosing (16); this mode of administration is likely to reduce pain, improve patient convenience and adherence to therapy, and ultimately improve long-term clinical outcomes (17).

The most important advantage of concizumab is its broad applicability across hemophilia subtypes. Its mechanism of action appears to be similar in both hemophilia A and hemophilia B, irrespective of inhibitor formation. For patients with hemophilia B who have inhibitors, this is a highly essential issue, since there are few treatment options available. Concizumab, in fact, represents an important step toward better managing hemophilia and providing a flexible, effective, and user-friendly option for patients (18).

CLINICAL EFFICACY AND SAFETY:

Studies in rabbit models demonstrate that the monoclonal antibody mab2021 was effective in reducing bleeding (19). Additionally, concizumab showed higher bioavailability after subcutaneous administration in cynomolgus monkeys (16). The same study also showed that concizumab has an elimination half-life of 0.14 mL/h/kg and achieves steady state levels within 7 days. Due to clearance-mediated target saturation, steady state can be achieved more slowly when the drug is administered every day. Research has shown that concizumab promotes clotting by neutralizing TFPI inhibition in a human endothelial cell-like immortalized cell line (20). Animal studies in hemophilic rat models also support the efficacy of concizumab as a prophylactic agent for hemophilia (21). Furthermore, findings from combination studies with concizumab and rFVIIa have reinforced its safety profile and effectiveness in reducing bleeding in in-vitro and animal models (22).

In the first human dose, phase 1 trial, escalating single doses of IV or subcutaneous concizumab were administered to healthy volunteers and individuals with hemophilia (23). Concizumab demonstrated a favorable safety profile for both SC and IV administration. No significant alterations in common coagulation parameters were reported. A dose-dependent procoagulant effect, substantiated by elevated D-dimer and prothrombin fragment 1 and 2 levels, was noted. Non-linear pharmacokinetics were observed, attributed to target medicine clearance.

In an ex vivo spiking study, platelet-poor plasma from 18 severe hemophilia patients exhibited a dose-dependent increase in thrombin generation when spiked with concizumab, reaching near-normal levels, emphasizing concizumab's potential as a novel therapeutic option for hemophilia (24).

Explorer 3, a phase Ib multiple-dose escalation study, evaluated the safety of subcutaneous concizumab in patients with severe hemophilia A without inhibitors (14). The study revealed a pharmacodynamic association between unbound tissue factor pathway inhibitor levels and thrombin generation. It investigated 3 dose cohorts, with 24 patients randomized 3:1 to receive either concizumab or placebo. The participants received 12 doses during the 42-day period. The pharmacokinetics of concizumab were non-linear

with respect to exposure. Higher D-dimer and F1+2 levels were observed in the highest-dose cohort, along with a dose-dependent decrease in TFPI levels and enhanced thrombin generation.

Clinical evidence for the use of subcutaneous concizumab as prophylaxis in hemophilia A/B with inhibitors, as well as in severe hemophilia A without inhibitors, was established by the two phase 2 trials, Explorer 4 and Explorer 5 (25). A starting dose of concizumab of 0.15 mg/kg was administered to patients and could be increased to 0.20 mg/kg or 0.25 mg/kg if a patient experienced ≥3 spontaneous bleeds within a 12-week period. Reduced annualized bleeding rates (ABR) were reported in the main trial results for patients with inhibitors (3.0 for hemophilia A inhibitors and 5.9 for hemophilia B inhibitors), compared with hemophilia A (7.0). Concizumab was well tolerated, and ADA was detected in three patients. In the extension studies, patients continued to receive concizumab, and the outcomes were consistent with those of the main trial, indicating sustained efficacy (26). The ABRs were 4.8 for EXPLORER4 and 6.4 for EXPLORER5, while the spontaneous ABRs were 1.8 and 2.1, respectively. Furthermore, ADA was detected in 25% of patients, but they were of low titer, transient, and clinically insignificant.

The Explorer7 was a phase 3 trial evaluating the safety and efficacy of concizumab in patients with hemophilia A or B and inhibitors (13). Patients were randomly assigned to receive no prophylaxis or concizumab prophylaxis for 32 weeks. In addition, two non-randomized groups received concizumab for at least 24 weeks. One patient developed a renal infarct as a result of nonfatal thromboembolic events, which led to a halt in the clinical trial. Following treatment pause as a result of nonfatal thromboembolic events in three patients (one patient from Explorer7), concizumab therapy was reinitiated at a dose of 1.0 mg/kg followed by a maintenance daily dose of 0.2 mg/kg, adjusted according to plasma concentration. The estimated mean ABR (± 95% CI) was 11.8 (± 0.47) episodes in the control group alone, versus 1.7 (± 0.38; P < 0.001) episodes in group 2, in which patients received concizumab prophylaxis. Mild and moderate breakthrough bleeding in hemophilia A/B patients with inhibitors was managed with a single injection of recombinant activated factor VII, along with factor VIII and IX for hemophilia A and B, respectively. Also, the overall median ABR for patients receiving concizumab (groups 2, 3, 4) was zero episodes. Concizumab was highly effective in reducing spontaneous bleeding in patients with hemophilia, with no further thromboembolic events reported after treatment was resumed.

Explorer 8 is a phase 3a study that evaluated concizumab in patients with severe hemophilia A/B without inhibitors (27). Two patients experienced non-fatal thromboembolic events that led to a halt of the study, which restarted with an adjusted dosing regimen. One of the subjects developed acute myocardial infarction, and another established deep vein thrombosis, pulmonary embolism, and superficial vein thrombosis. In total, 173 patients were screened, and 148 were randomized to four groups after the trial continued. Group 1 continued to receive on-demand clotting factors without prophylaxis, whereas group 2 received prophylaxis with concizumab. The estimated mean ABR ratio for treated spontaneous and traumatic bleeding episodes during concizumab prophylaxis versus the control group was 0.14 for patients with hemophilia A and 0.21 for those with hemophilia B. A treatment-related serious AE (intra-abdominal hemorrhage) occurred. All three patients who experienced thromboembolic events had established risk factors, including smoking, hypertension, occasional chest pain, and high BMI. In addition, these three patients had exposure to concomitant hemostatic medication and higher plasma concizumab concentrations prior to the event onset. No thromboembolic events were reported following trial restart.

Phase 3a, open-label, multicenter clinical trial, Explorer 10 (NCT05135559), is currently assessing the safety and long-term effectiveness of concizumab as a once-daily subcutaneous prophylaxis for hemophilia A or B in the pediatric

population. A retrospective cohort study in children below 6 years of age having severe HB, along with inhibitors, was given concizumab prophylaxis for 12 weeks. Analysis of thrombin generation revealed significant improvement after exposure and a decline in FIX inhibitor levels. ABR ranged from 0-4, and spontaneous bleeding occurred in 2 of 5 patients, following which dose adjustments were indicated (28).

CURRENT THERAPEUTIC LANDSCAPE BEFORE THE INTRODUCTION OF CONCIZUMAB

In response to the growing need for more effective and convenient treatments for hemophilia, multiple novel therapies have been developed in recent years to provide alternatives to standard factor replacement therapy. Before the development of concizumab, treatments with the most promising results and improved patient outcomes include non-factor therapies such as emicizumab and fitusiran, as well as gene therapy.

1) Emicizumab

A frequently used drug is emicizumab, which is a recombinant bispecific IgG antibody. It works by mimicking factor VIII and binding to factors IX and X to restore the coagulation cascade, thereby enhancing clot formation (29). Emicizumab achieves a >90% reduction in annualized bleeding rate (ABR) compared to no prophylaxis and demonstrates efficacy even at a less frequent dose, offering flexibility and patient convenience (30). Clinical trials on the pediatric population reveal that following emicizumab prophylaxis, 77% of patients experienced no bleeding episodes(31). Thrombotic microangiopathy and thrombotic events are rare complications that may occur in patients receiving concomitant therapy with emicizumab and aPCC(32). While on concizumab prophylaxis, breakthrough bleeds can be managed with bypassing agents without concern for a strong synergistic effect (33). Having a subcutaneous administration route, with once-weekly, once-monthly, or twice-monthly dosing, decreases the cost of frequent injections (34). Currently, it works for hemophilia A, with or without inhibitors, but has yet to show any positive results for hemophilia B. Concizumab, on the other hand, works for both HA and HB and is hence a better drug of choice. Moreover, long-term safety and efficacy data are still emerging from research (35).

2) Gene Therapy

Gene therapy is a one-time IV infusion of a functional copy of the gene that enables the body to generate its own clotting factor, reducing dependence on factor replacement therapy. It uses an Adeno-Associated virus (AAV) vector to deliver the therapeutic gene (F8 or F9) into patients' hepatocytes (36). Recombinant AAV (r-AAV) is an altered form of the viral genome that contains the desired gene sequence. This is effective for both Hemophilia A and B but is limited to patients without inhibitors, with Hemgenix and Roctavian approved by the FDA for hemophilia A and B, respectively, in adults (37). Gene therapy reduces the frequency of bleeding episodes for 1 to 3 years post-treatment, and follow-up studies are needed to further evaluate the long-term efficacy. However, some limitations persist, including a short duration of effect, high cost, and susceptibility to neutralization by pre-existing antibodies (35,36). As a result of these challenges, it is not likely to become a standard treatment. In spite of that, recently, platelet-targeted gene therapy using the ITGA2B gene promoter in a patient of Hemophilia A with Factor VIII inhibitors was shown to safely and effectively decrease ABR from 10 to 0 in the 24-month follow-up period, along with showing feasibility and safety, though long-term and diverse population data are still awaited (37). On the other hand, concizumab is a safer and more effective alternative because it generates results for both inhibitor-positive and inhibitor-negative patients (35).

3) Fitusiran

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Another interesting approach for hemophilia is fitusiran, which is a GalNAc-siRNA conjugate. It works by preventing antithrombin production, which acts as an anticoagulant for factors II, IX, X, XI, and XII, while increasing thrombin generation and promoting homeostasis. Also administered subcutaneously once a month, due to its long half-life, it reduces treatment costs (38). It has been shown to reduce ABR compared to on-demand treatment for both HA and HB, with and without inhibitors (39). However, there is a high risk of thrombosis in case of overdose of fitusiran. While concizumab also reported thromboembolic events in EXPLORER 7 and 8 trials, leading to temporary pauses and dose adjustments, no new events were observed after dosage regimen modification, making it a more favorable and safer option with an overall similar drug profile (13,27,40).

4) Recombinant Activated FVII (rFVIIa)

Recombinant activated factor VII (rFVIIa) is a vitamin-K-dependent clotting factor developed for people with hemophilia who have developed inhibitors and can no longer use factor replacement products(41). Two rFVIIa products are currently approved by the FDA for the management of hemorrhagic episodes, namely, eptacog alpha and eptacog beta. rFVIIa exerts its hemostatic effect by enhancing thrombin generation through its binding to thrombin-activated platelets at the site of injury, thus bypassing the need for the deficient factors(42). However, one of its limitations is the short dosage interval required to achieve optimal therapeutic concentration. The dose administered is markedly higher than the physiological level, with a plasma half-life of 2.5 hours (43). Concomitant use of rFVIIa in patients who were on emicizumab was well tolerated apart from an infant who died after developing a large, unsalvageable retroperitoneal hematoma(44). While the majority of other clotting factor products are inactive precursor proteins, rFVIIa, conversely, is an activated form of CF, and its use in the treatment of breakthrough bleeds has been associated with an increased risk of thromboembolic events(45).

Table 1: Comparison of Concizumab Prophylaxis and Existing Treatments for Hemophilia A or B With or Without Inhibitors.

Parameter	Concizumab	Factor Replacement	Emicizu-mab	Fitusiran	Gene Therapy
Treatment Type	Monoclonal antibody (anti TFPI)	Clotting factor replacement	Bispecific monoclonal antibody	siRNA targeting antithrombin	AAV-mediated gene therapy
Mechanism of Action	Inhibits TFPI → ↑ thrombin generation	Replaces deficient FVIII or IX	Bridges FIXa and FX (mimicking Factor VIII activity)	Reduces antithrombin → ↑ coagulation	Delivers functional clotting factor gene
Indication	Hemophilia A & B (± inhibitors)	Hemophilia A & B	Hemophilia A (± inhibitors)	Hemophilia A & B (± inhibitors)	Hemophilia A & B (depending on therapy)
Route of Administration	Subcutaneous	Intravenous infusion	Subcutaneous	Subcutaneous	Intravenous (single dose)
Efficacy	↓ bleeding events, improved QoL	Effective in preventing bleeding	Reduces bleeding, suitable for inhibitors	↓ bleeding via antithrombin suppression	Sustained ↓ bleeding via factor expression
Safety Profile	Thrombosis risk, injection reactions, ↑ liver enzymes	Inhibitor development, allergic reactions	Thrombotic microangiopathy (rare)	thrombosis risk, liver toxicity	immune responses to viral vector, ↑ liver enzymes
Dosing Frequency	Daily/less frequent	2-3 times per week or on demand	Weekly to monthly	Monthly	One-time infusion
Regulatory State	Approved (FDA, December 20, 2024) Alhemo	FDA-approved; standard of care	FDA-approved	FDA-approved	Specific therapies approved for hemophilia A & B, (Valoctocogene roxaparvovec for hemophilia A).
Limitations	Long-term safety still being studied	Frequent infusions; inhibitor risk	Not suitable for hemophilia B	Requires monitoring for thrombosis	High cost, long-term risk unknown

Overall, these therapies have improved the treatment landscape for hemophilia over the years, with each one significantly reducing the ABR, making administration easier, and expanding options for patients with inhibitors. Despite this, their widespread adoption was limited by challenges such as thrombotic risks, variable or unavailable long-term data, and high treatment costs. These gaps highlighted the need for a therapy that is effective across different hemophilia subtypes and inhibitor profiles and is safe and feasible in clinical practice. A comparative overview of emicizumab, gene therapy, fitusiran, and concizumab is presented in Table 1.

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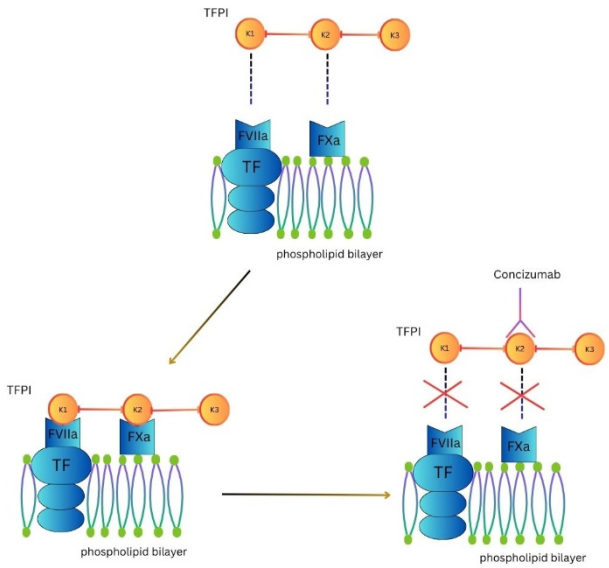
Figure 1: Diagram showing TFPI (K1, K2, K3 domains) regulating coagulation on the phospholipid bilayer. The K1 domain inhibits the TF–FVIIa complex, and the K2 domain inhibits FXa. In the presence of concizumab, the antibody binds to the K2 domain of TFPI, block



DISCUSSION:

The pharmaceutical profile of concizumab, including its pharmacokinetics and pharmacodynamics, is crucial for understanding its effectiveness in treating hemophilia. Concizumab exhibits complex behavior in the body, including its uptake and metabolism within cells. It shows a dose-dependent, non-linear pharmacokinetic (PK) profile (23), with slow clearance from the body due to its tendency to bind to mTFPI, resulting in endocytosis and degradation (46). Concizumab has a long half-life; however, higher doses are needed to effectively suppress sTFPI and prevent bleeding in hemophilia patients. Many researchers have proposed various models to support the idea that anti-TFPI recycling antibodies would be effective. These antibodies work by unbinding from mTFPI and sTFPI within cells (in endosomes), thereby preventing their breakdown. This helps the antibodies remain longer in the body and suppress TFPI more effectively, consequently reducing the amount of concizumab needed for the treatment of hemophilia (46). The pharmacodynamic effects of concizumab, as discussed above, have been presented in various trials, as it has proved to be an excellent drug for treating hemophilia by reducing the amount of free TFPI in the body, thereby eventually leading to thrombin formation (15,33,47).

Concizumab has been regarded as a great treatment for reducing the frequency of both spontaneous and traumatic bleeding episodes. As concizumab acts earlier in the coagulation pathway, it offers a more effective and better way to control bleeding than traditional replacement therapies (26). This is greatly beneficial for patients who have developed inhibitors to standard clotting factor treatments. Due to its ability to provide better control over bleeding, especially during surgeries or after trauma, it can improve patient outcomes and reduce the need for intensive care. Moreover, concizumab offers a convenient route of administration, as it can be given via subcutaneous injections at home, thereby avoiding the usual IV infusions and frequent hospital and clinic visits (25). This not only prevents uneasiness but also makes the entire procedure less stressful, improving the overall patient experience. In a recent trial, the use of a pen injector for subcutaneous administration of concizumab was highly encouraged. It is a pre-filled, multi-dose device with a 4 mm, 32 G needle. The purpose of this study was to understand the handling experience of patients and their caregivers with pen injectors as well as their preference for it over their current devices. The results showed that 98% of participants found it easy and convenient to use, whereas 88% preferred it over their current treatment method, indicating its successful acceptance by patients and caregivers (48). Subcutaneous drug administration can be helpful for treating younger patients with hemophilia due to its convenience. However, its administration in newborns is uncertain because newborns have a developing blood clotting system that may behave differently from that of older children or adults. For this reason, newborns were not included in the key clinical studies, leading to a lack of reliable data to clearly assess the safety or

effectiveness of these treatments in this age group (49).

The collective data from the Explorer trials support the efficacy and safety of concizumab in various hemophilia A and B populations, both with and without inhibitors (13,23,25,27). Early-phase studies showed dose-dependent suppression of TFPI and enhancement of thrombin generation (23), while later phase 2 and 3 trials demonstrated significant reductions in ABR (13,25,27). Although initial thromboembolic events led to protocol modifications, optimized dosing regimens have improved safety profiles without compromising efficacy (13,27). Notably, the observed variability in pharmacokinetic and pharmacodynamic profiles underscores the potential for individualized treatment approaches (23). By adjusting dosing based on bleeding phenotype, inhibitor status, and treatment response, concizumab may help achieve a more personalized, balanced prophylactic regimen with improved efficacy and an acceptable safety profile (13,25).

Although the efficacy and safety of concizumab have been well described through clinical trials, real-world evidence remains limited. A recent systematic review supports its favorable benefit–risk profile; however, long-term registry data and post-marketing surveillance studies are still required to assess safety, adherence, and effectiveness in broader, more heterogeneous patient populations outside controlled trial settings (50). Therefore, further ongoing observational studies are needed to determine its sustained clinical value in routine practice.

Despite proving to be a highly effective treatment for hemophilia, concizumab faces multiple barriers to widespread adoption. The most notable issue is competition with emicizumab and Gene therapy, which have already established themselves in the marketplace, making it difficult for concizumab to establish a base. Additionally, the high cost associated with concizumab presents a significant hurdle; long-term usage puts financial strain on patients and limits accessibility, particularly in low- and middle-income countries (51). While it offers a more convenient and potentially effective option compared to previous therapies, this financial burden may discourage healthcare workers from prescribing it (4). Moreover, formal cost-effectiveness and pharmacoeconomic data are limited. Evaluating the long-term economic value of concizumab, including potential reductions in hospital visits, improved adherence, and prevention of bleeding-related complications, would help clarify its overall benefit.

Concizumab is a prophylactic therapy rather than a curative treatment, so proper dosing and implementation are necessary (13). Furthermore, patients may struggle with self-administration due to insufficient education regarding the therapy and probable trypanophobia (51). Administering to children is challenging, as they may be reluctant to receive frequent injections (52). Therefore, educating caregivers and parents about proper administration techniques and the significance of adhering to the dosing regimens is important to prevent frequent bleeding episodes.

Although concizumab has been approved as a novel treatment, its availability across countries remains limited. Additionally, the production and distribution of new therapies take time, and developed countries receive priority availability before the treatment reaches low- and middle-income countries, where it is needed more. High costs hinder accessibility, with low- and middle-income countries at further disadvantage due to their economic status (53).

While clinical trials have proven the efficacy of concizumab, unanticipated adverse events have been reported. Some of the more severe incidents include intra-abdominal hemorrhage, with long-standing hypertension, as well as deep vein thrombosis and injection site pain. However, further advancements have decreased the incidence of such events (27). Nonetheless, concerns persist regarding the long-term safety (12,13) and potential adverse effects, such as hypersensitivity reactions and

thromboembolic events (27). Routine monitoring might prove effective, but it can impose a financial strain on patients (13). Therefore, improving cost-effectiveness, educating patients and caregivers, and monitoring to ensure safety are important to make concizumab a more accessible and safe choice for the treatment of hemophilia.

FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS:

MG1113, another TFPI inhibitor, increased peak thrombin and endogenous thrombin levels. In patients treated with MG1113, rotational thromboelastometry assays showed restoration of normal values for clotting time, clot formation time, and maximum clot firmness (54). MG1113 lowered free TFPI more quickly when given IV versus SC. The pharmacokinetic and pharmacodynamic effects of MG1113, supported by clinical dose optimization, were successfully predicted by a feedback model, validated in monkeys, and applied to humans (55). This further strengthens the rationale for concizumab, a TFPI inhibitor, being highly effective.

Concizumab's potential for treating bleeding disorders has already been demonstrated by multiple clinical trials and studies. Although research and studies are still ongoing to examine its potential and efficacy. A study is being conducted to evaluate concizumab's effectiveness in stopping bleeding in patients with hemophilia. The long-term study is expected to last for about six years. Using a pen injector, participants will self-inject the medication and record their experience in an electronic diary. In this trial, patients are randomly assigned to receive either concizumab or no treatment. The main trial phase duration is 24-32 weeks in arm 1 participants and in arm 2-4 participants, respectively. Participants will remain in the trial until concizumab becomes readily available, expected in November 2025 (56).

The progress of new novel therapies in recent years has been helpful for hemophilia patients, improving their treatment. Concizumab is helping to facilitate the development of novel therapies for hemophilia. Concizumab and rFVIIIa are used in the treatment of patients with hemophilia to promote clot formation and platelet accumulation. When concizumab and rFVIII are allowed to work together, remarkable benefits are seen, explaining 78-94% of the observed effects, in which 20% of these effects are due to positive drug-drug interactions (33).

Activated prothrombin complex concentrate (APCC) and concizumab worked well together, and the results were highly effective, accounting for 68-83% of the observed impacts; however, increasing concizumab didn't seem to increase benefits; instead, the effects were primarily additive. When rFIX and concizumab were used together, a minor decrease of up to 10% in rFIX's effect was observed due to negative drug-drug interactions (33). The idea of combining concizumab and emicizumab is currently being studied, and no studies have been published yet, but it is expected that their combination will be very helpful.

Other diseases can also demonstrate the effectiveness of concizumab in their treatment. One of the diseases in which TFPI levels are high is Factor V East Texas bleeding disorder (FVETBD). Inhibition of TFPI using any monoclonal antibody against it or recombinant FVIIIa in a dose-dependent manner could help restore thrombin generation; thus, concizumab, which works as a TFPI inhibitor, can be helpful in the treatment of these patients (57). Overall, concizumab is an important addition to non-factor therapies for hemophilia. Ongoing studies and post-marketing data will help define its long-term safety, optimal dosing, and place in future treatment strategies.

CONCLUSION:

Concizumab is a humanized monoclonal antibody that blocks TFPI. It helps restore thrombin generation in patients with hemophilia A and B, whether or not they have inhibitors. Clinical trials, including Explorer 7 and 8, show that it significantly

reduces bleeding rates while maintaining manageable safety. There have been no thromboembolic events since the trials resumed. Compared with emicizumab and fitusiran, concizumab is effective for both types of hemophilia and has a lower risk of thrombosis. Its early action in the coagulation pathway and its ease of subcutaneous administration make it practical for patients with inhibitors. Challenges include the cost and the need for training on self-administration. Research is required to develop personalized treatment and combination therapy with concizumab.

Abbreviations:

HA: Hemophilia A; HB: Hemophilia B; CNS: Central Nervous System; TF: Tissue Factor; IV: Intravenous; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; TFPI: Tissue Factor Pathway Inhibitor; FXa: Factor Xa; FVIIa: Activated Factor VIIa; ABR: Annualized Bleeding Rates; AAV: Adeno-Associated Virus; PK: Pharmacokinetic; TGA: Thrombin Generation Assay; r-AAV: Recombinant Adeno-Associated Virus; APCC: Activated Prothrombin Complex Concentrate; FVETBD: Factor V East Texas Bleeding Disorder; S/C: Subcutaneous; AE: Adverse Effects; AT: Antithrombin; CAD: Coronary Artery Disease; mAB: Monoclonal Antibody

DECLARATIONS:

- Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
- Authors' contributions: SJF, SHF, AA, MF, and SVB contributed to original writing and editing. AyA conceptualized, edited, reviewed, and critically revised the manuscript. AyA, RA, and RKM reviewed and edited. All authors have read and agreed to the final version of the manuscript.
- Funding: No funding was acquired for this paper.
- Acknowledgements: Not applicable

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