Hemophilia: changes and new achievements in management and care

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ABSTRACT

Hemophilia treatment has changed significantly in recent years, progressively improving patients' quality of life and offering more promising therapeutic approaches, with the ambitious goal of achieving a "hemophilia-free mind." Bleeding prevention through regular administration of a hemostatic agent (prophylaxis) represents the gold standard treatment to enable affected individuals to lead an active life, comparable to that of the general population. For replacement therapy, extended half-life FVIII and FIX concentrates have been developed, allowing an extension of the time between intravenous administrations and improving adherence to treatment. These new clotting concentrates allow treatment personalization, making it possible to reduce the number of infusions or increase the protection, maintaining higher circulating levels of FVIII or FIX, based on the characteristics and needs of the individual patient. Advances in understanding of the underlying molecular mechanisms have led to the development of therapeutic strategies to promote or improve hemostasis, through generation of thrombin without the need for FVIII or FIX. This represents a promising therapeutic option for patients with and without inhibitors. The molecules that form the basis of non-replacement therapy have the advantage of being administered subcutaneously, have a long half-life, are suitable for long-term prophylaxis, and provide constant protection. Only the humanized bispecific FVIII mimetic antibody emicizumab is already available in clinical practice. The other molecules are aimed at rebalancing hemostasis, by interacting with different physiological mechanisms of anticoagulation (monoclonal anti-TFPI antibodies and an RNA interference molecule able to decrease antithrombin transcription). Finally, gene therapy, which aims to correct the genetic defect underlying hemophilia, represents one of the most promising frontiers.

KEYWORDS

Hemophilia, arthropathy, prophylaxis, quality of life.

Introduction

Hemophilia is a rare inherited bleeding disorder caused by deficiency or functional abnormality of either clotting factor VIII (FVIII), in hemophilia A (HA), or IX (FIX), in hemophilia B (HB). HA is more common than HB, with a prevalence of one in 5,000-10,000 male live births compared with one in 30,000, respectively. HA and HB are transmitted genetically as X-linked recessive disorders [1]. The severity of the disease is classified according to the plasma level of FVIII or FIX activity, which is determined by the type of causative mutation in *F8* or *F9*. Although the bleeding phenotype may be rather heterogeneous, severe disease is defined as a factor level < 1 IU/dL; moderate disease as 1-5 IU/dL, and mild disease as 6-40 IU/dL [2] (Table I). Severe hemophilia is characterized by spontaneous bleeding into joints or muscles at an early age and bleeding after minimal trauma, whereas in moderate or mild hemophilia bleeding predominantly occur after trauma or

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Table I Clinical classification of hemophilia A and B.

CLASSIFICATION	FVIII OR FIX ACTIVITY	CLINICAL MANIFESTATIONS
Severe	<1 IU/dL	Spontaneous bleeding from early infancy Frequent spontaneous hemarthroses, soft-tissue and post-trauma or surgical bleeding
Moderate	1-5 IU/dL	Bleeding mainly after trauma or surgery Occasional spontaneous hemarthroses
Mild	>5-40 IU/dL	Bleeding after trauma or surgery Rare spontaneous hemarthroses

surgery. Recurrent joint bleeding leads to cartilage and bone destruction, resulting in hemophilic arthropathy, responsible for chronic pain, disability, and a negative impact on patients' quality of life (QoL). In around half of children with severe hemophilia, joint bleeding first occurs during the first year of life [3], and 90% of patients experience at least one joint bleeding episode before the age of 4.5 years [4]. Eighty per cent of joint bleeding episodes involve the knees, elbows, and ankles [5], with multiple sites often becoming target joints. Joint bleeding with pain and associated functional limitations are also responsible for reduced physical activity resulting in decreased bone mineralization and increased susceptibility to fractures. Deep muscles are also frequent target sites, where bleeding can potentially impair function. Bleeding into the ilio-psoas muscles and retroperitoneal space can be life-threatening when a large volume of blood in the peritoneum is lost. In addition, femoral nerve compression with permanent disability can occur if a compartment syndrome develops. Bleeding into a closed fascial compartment can lead to compression of vital structures resulting in a compartment syndrome characterized by ischemia, gangrene, flexion contractures, and neuropathy. Life-threatening bleeding, such as intra-cerebral [6], intra-abdominal, or gastrointestinal hemorrhages, may also occur.

The natural history of hemophilia has changed profoundly in recent years due to advances in treatment and medical care. Historically, severe hemophilia has been associated with short life expectancy, with high mortality rates due to uncontrolled bleeding and complications, the condition being worse in patients who, as a complication of hemophilia treatment, develop alloantibodies against FVIII or FIX, able to neutralize their clotting activity (inhibitors). The cumulative incidence of this complication, which usually arises within the first 10-15 days of exposure, appears to be 20-40% in HA, and less than 5-10% in HB. Management of the bleeding is difficult and involves the use of bypassing agents (recombinant [r-] activated factor VII or activated prothrombin complex concentrates), when the inhibitory titer is high (>5 Bethesda Units/mL), with suboptimal efficacy in bleeding management and prevention. Today, the average life expectancy of individuals with hemophilia has increased dramatically, becoming comparable to that of a healthy population. QoL has also improved significantly, with fewer bleeding episodes, reduced joint damage, and greater independence, and most younger patients are able to lead more normal lives. People with hemophilia can attend school, hold jobs, and participate in sports and physical activities, all of which were once difficult or impossible. These improvements are due not only to the increased availability of more advantageous therapeutic options, but also to the possibility of personalizing treatment.

Prophylaxis treatment

The mainstay of hemophilia treatment is replacement of missing clotting factors, administered either on demand or as prophylaxis, to prevent or reduce the risk of bleeding [1]. Prophylaxis is the cornerstone of hemophilia management [7] and the World Federation of Hemophilia [8] strongly recommends long-term prophylaxis for patients with severe clinical phenotypes. Prophylaxis should be individualized on the basis of not only bleeding phenotype, but also joint status, individual pharmacokinetics, patient self-assessment, and preference. Primary prophylaxis with regular infusions of factor concentrates, initiated early, prior to the onset of joint disease and ideally before the age of 3, is the standard of care for pediatric patients. Guidelines on prophylactic treatment in adulthood are less clear, although the benefits seem to be indisputable, resulting in a significant reduction of bleeding episodes per year and better QoL [9,10]. Moreover, in elderly patients prophylaxis may be administered with the aim of protecting against bleeding related to comorbidities or to therapies for their management, such as anti-platelet or anticoagulant treatments in cardiovascular disease [11], which is an emerging medical issue in this population, with a prevalence of 15% [12].

The current therapeutic options for prophylaxis are replacement or non-replacement therapy and gene therapy (GT).

Replacement therapy

The etiological treatment of hemophilia involves replacing the missing blood clotting factor through intravenous infusion of clotting factor concentrates, so that the blood can clot properly. Plasma-derived or recombinant FVIII and FIX concentrates are widely available. The dosing of replacement therapy is based on several factors including age, lifestyle, circulating half-life (HL) of plasma FVIII and FIX, and the level of activity required to achieve adequate hemostasis or prophylaxis. In the case of endogenous FVIII and FIX, the circulating HL is 8-12 and around 18 hours, respectively. Available r-FVIII and r-FIX concentrates can have either a standard (SHL) or an extended (EHL) HL. Different technologies are applied to extend HL, such as conjugation with polyethylene glycol and the production, by genetic engineering, of fusion proteins containing FVIII and FIX linked to a long-lived plasma protein such as the Fc fragment of immunoglobulin (Ig)G or albumin, the latter, available for FIX only (Tables II and III). The HL of r-FIX can be extended considerably, even reaching 100 hours. Due to its greater size and the ceiling influence of endogenous von Willebrand factor (VWF), which is the FVIII carrier, the effect in r-FVIII products so far is only moderate, with the HL extended to about 15-18 hours.

Prophylaxis regimens with SHL-FVIII and SHL-FIX are based on a dosing schedule determined by patient body weight, and two or three infusions per week are required to maintain protective factor trough levels > 1-2 IU/dL of the missing factor. The availability of EHL concentrates has made it possible to reduce infusion frequency, with the interval extended to 3-5 days in HA and 7-14 days in HB. It has thus become easier to identify personalized prophylactic regimens in terms of dose, trough levels of 3-5 IU/dL, and infusion scheduling [13,14] (Tables II and III).

Significant benefits for HA patients will probably become possible with efanesoctocog alfa, a novel r-FVIII product, not yet approved, that is coupled to VWF and thus independent of endogenous VWF [15]. Several modifications have been made to extend its plasma HL, giving three- to four-fold longer he-

Table II Standard and extended half-life r-FVIII concentrates available in Italy, with recommended regimens for prophylaxis.

PRODUCT	CHARACTERISTIC	PROPHYLAXIS REGIMEN ACCORDING TO DATA SHEET
SHL FVIII concentrates		
Octocog alfa (Recombinate®)	First generation full-length r-FVIII	20-40 IU/kg at 2- to 3-day intervals
Octocog alfa (Advate®)	Third generation full-length r-FVIII	20-40 IU/kg at 2- to 3-day intervals < 6 years: 20-50 IU/kg 3-4 days per week
Moroctocog alfa (Refacto AF®)	Second generation B domain-deleted r-FVIII	20-40 IU/kg at 2- to 3-day intervals
Octocog alfa (Kovaltry®)	Full-length r-FVIII with superior glycosylation	20-40 IU/kg 2-3 times a week < 6 years: 20-50 IU/kg 2-3 days per week or every other day
Turoctocog alfa (Novoeight®)	B domain-truncated r-FVIII fully sulfated at Tyr1680	20-40 IU/kg every 2 days or 20-50 IU/kg 3 days a week Adults and adolescents also: 40-60 IU/kg every 3 days or two days a week
Simoctocog alfa (Nuwiq®)	B domain-deleted r-FVIII fully sulphated with preserved N-glycosylation. Only r-FVIII produced by human cell line	20-40 IU/kg at 2- to 3-day intervals
Lonoctocog alfa (Afstyla®)	Single-chain r-FVIII with stronger affinity to VWF	20-50 IU/kg 2-3 days per week Pediatric patients: 30-50 IU/kg 2-3 days per week
EHL FVIII concentrates		
Efmoroctocog alfa (Elocta®)	Fusion protein with the Fc fragment of IgG1 (r-FVIIIFc)	50 IU/kg at 3- to 5-day intervals Dose can be adjusted in a range between 25 and 65 IU/kg Children under the age of 12 may need higher or more frequent doses
Rurioctocog alfa pegol (Adynovi®)	Random PEGylation of r-FVIII	40-50 IU/kg twice a week at intervals of 3-4 days. Adjustments of doses and intervals between doses can be considered based on FVIII levels achieved and individual bleeding phenotype.
Damoctocog alfa pegol (Jivi®)	Site-specific PEGylation	45-60 IU/kg every 5 days. Depending on the clinical characteristics of the patient, the dose could also be 60 IU/kg every 7 days or 30-40 IU/kg twice a week In overweight patients, the maximum prophylactic dose per infusion should not exceed 6,000 IU.
Turoctocog alfa pegol (Esperoct®)	Single site-specific PEGylation of r-FVIII	50 IU per kg of body weight every 4 days. Dose adjustments and dose intervals can be considered based on factor VIII levels and individual bleeding tendency.

Table III Standard and extended half-life rFIX concentrates available in Italy, with recommended prophylaxis regimens.

PRODUCT	CHARACTERISTIC	PROPHYLAXIS REGIMEN ACCORDING TO DATA SHEET
SHL-FIX concentrates		
Nonacog alfa (Benefix®)	Third-generation r-FIX	40 IU/kg every 3-4 days. In some cases, especially in younger patients, shorter or longer dosing intervals may be required.
Nonacog gamma (Rixubis®)	Third-generation r-FIX	Patients > 12 years: 40-60 IU/kg every 3-4 days Patients < 12 years: 40-80 IU/kg every 3-4 days
EHL-FIX concentrates		
Albutrepenonacog alfa (Idelvion®)	Fusion protein with albumin fusion (r-FIX-FP)	Patients > 12 years: 35-50 IU/kg once a week. Some patients who show optimal control of the disease with once-weekly administration may, with a dose of up to 75 IU/kg, switch to administration once every 10 or 14 days. Patients <12 years: 35-50 IU/kg once a week For patients > 18 years of age, further extension of the range of administration may be considered.
Eftrenonacog alfa (Alprolix®)	Fusion protein with the Fc fragment of IgG1 (r-FIXFc)	Patients > 12 years: 50 IU/kg once a week, adjusting the dose according to individual response, or 100 IU/kg once every 10 days, adjusting the interval according to individual response. Patients < 12 years: 50-60 IU/kg every 7 days. Some well-controlled patients with a once-every-10-day regimen may possibly be treated at intervals of 14 days or more.
Nonacog beta pegol (Refixia®)	Site-specific glycoPEGylation of r-FIX	Not approved for patients < 12 years. 40 IU/kg body weight once a week. Dose and interval adjustments may be considered based on FIX levels and individual bleeding tendency.

mostatic control, and allowing high FVIII trough levels (of between 10 and 40 IU/dL) to be maintained with 50 IU/kg once-weekly administration [16].

However, despite the significant improvements achieved, the management of long-term prophylaxis continues to pose several clinical challenges. The frequency of intravenous administrations and the accessibility of suitable veins can still be particular issues, closely related to adherence and possible occurrence of breakthrough bleeding [17].

Non-replacement therapy

Improved understanding of the underlying molecular mechanisms has enabled the development of therapeutic strategies that promote hemostasis by enhancing defective thrombin generation (TG) independently of FVIII or FIX. The new agents developed act by mimicking FVIIIa (emicizumab, mim8) or by inhibiting natural anticoagulant pathways (concizumab, fitusiran) [18]. Emicizumab and mim8 are humanized recombinant bispecific antibodies with specificity for activated FIX (FIXa) and factor X (FX) [19]. They act as a bridge between FIXa and FX, mimicking the activity of FVIII *in vivo* and generating FXa, required for the conversion of prothrombin to thrombin. Another strategy to improve TG is reduction of antithrombin (AT) activity by using RNA interference, i.e., the natural process of gene silencing. The small interfering RNA fitusiran works by suppressing hepatic synthesis of AT [20]. It binds and degrades AT mRNA in hepatocytes, leading to posttranscriptional silencing of *AT* gene expression and hence prevention of AT synthesis. Reduction in AT levels leads to increased availability of thrombin, FXa, and FIXa. Another way to induce TG is by using the anti-TFPI humanized recombinant antibodies concizumab or marstacimab to inhibit the tissue factor (TF) pathway inhibitor (TFPI). TFPI is a multivalent Kunitz-type serine protease inhibitor that consists of three domains with different roles. Domain 1 binds to the TF-FVIIa complex, domain 2 acts on activated FXa, and domain 3 interacts with protein S (PS). TFPI exerts its anticoagulant effects by inhibiting the TF-FVIIa complex as well as early forms of the prothrombinase complex [21]. TFPI inhibition leads to increased availability of the FVIIa/TF complex, which produces a larger amount of FIXa and FXa, ultimately increasing TG (Table IV). Advantages of these products are their subcutaneous route of administration and long HL, with the exception of concizumab, which is administered daily. These agents could improve compliance and protection and can be used in patients with and without inhibitors. Once the steady state is reached, constant protection is guaranteed, without the typical peaks and troughs of replacement therapy. They represent optimal therapeutic options for long-term prophylaxis treatment, but the protection they confer is not absolute and association with coagulation concentrates may be necessary.

The co-administration of replacement therapy for the treatment of breakthrough bleeds or the management of post-trauma and surgery is one of the most important issues, as it could lead to excessive TG and increased prothrombotic risk [22] (Table V).

Emicizumab (Hemlibra, Roche Genentech, South San Francisco, CA, USA) is currently the only biologic agent worldwide approved and available in clinical practice for routine prophylaxis in patients with and without inhibitors. It is administered as a single subcutaneous injection weekly, or every two or four weeks. Clinical trials and real-world data have consistently demonstrated a significant reduction in annual bleeding rates and the resolution of more than 95% of target joints; many patients experienced zero bleeding episodes with a clear improvement in QoL [23-25]. All other molecules are at various advanced stages of study [26-28] and have shown excellent efficacy, with significant reduction of bleeding and QoL improvement. With regard to safety, rare thromboembolic events (TEs) have occurred with all molecules in the different clinical trials. TEs were never spontaneous but were associated with co-administration of replacement therapy and the presence of other prothrombotic risk factors. A review of the treatment patterns with coagulation concentrates was necessary to mitigate this risk, indicating appropriate dosages and treatment durations. In addition, non-neutralizing anti-drug antibodies (ADAs) against concizumab and emicizumab have been reported. However, ADAs with neutralizing potential against emicizumab were observed in < 1% of participants only, and none in those treated with the other agents.

Table IV Novel therapeutic approaches.

MECHANISM OF ACTION	PRODUCT (GENERIC NAME)	COMPANY	TARGET POPULATION	STATUS
Humanized bi-specific monoclonal antibody mimicking FVIII	emicizumab	Roche Genentech	Severe HA patients with and without inhibitors; moderate HA patients with severe bleeding phenotype	Approved
Humanized bi-specific monoclonal antibody mimicking FVIII	mim8	Novo Nordisk	HA patients with and without inhibitors	Phase 3 clinical trial
Humanized monoclonal antibody against TFPI	concizumab	Novo Nordisk	HA and HB patients with and without inhibitors	Phase 3 clinical trial. Approved in Canada for HB patients with inhibitors
Humanized monoclonal antibody against TFPI	marstacimab	Pfizer	HA and HB patients with and without inhibitors	Phase 3 clinical trial Approved by EMA
siRNA against AT mRNA	fitusiran	Sanofi Genzyme	HA and HB patients with and without inhibitors	Phase 3 clinical trial Approved by FDA

Legenda: **FVIII**, factor VIII; **TFPI**, tissue factor pathway inhibitor; **AT**, antithrombin; **HA**, hemophilia A; **HB**, hemophilia B.

Table V Comparison between replacement therapy and non-replacement therapy in hemophilia.

	REPLACEMENT THERAPY	NON-REPLACEMENT THERAPY
Mechanism	Designed to provide the missing clotting factor (FVIII for HA, FIX for HB) into the bloodstream.	Designed to achieve hemostasis through different mechanisms, by targeting other parts of the coagulation cascade or by rebalancing the pro-clotting and anti-clotting factors in the blood.
Drugs	**Standard half-life (SHL) factor concentrates:** Require more frequent infusions as they are cleared from the body relatively quickly. **Extended half-life (EHL) factor concentrates:** Modified to stay in the body longer, allowing for less frequent infusions (e.g., once or twice a week, or even less frequently in HB).	**Bispecific antibodies (e.g., emicizumab):** These antibodies mimic the function of FVIII by bringing together Factor IXa and Factor X, allowing the clotting process to proceed. **Rebalancing agents:** These therapies aim to shift the balance towards clotting by inhibiting natural anticoagulants: fitusiran (inhibits antithrombin) and concizumab (inhibits tissue factor pathway inhibitor - TFPI). Those therapies are in various stages of development or approval.
Administration	Intravenous	Subcutaneous
Pharmacokinetic	Characteristic peaks (high hemostatic protection) and troughs (low protection with risk of bleeding).	At the steady state constant protection, but not absolute
Indications	Long-term prophylaxis and on–demand treatment	Long-term prophylaxis
PROS	**Directly addresses the deficiency:** Provides the exact missing protein, allowing the blood clotting cascade to function more normally. **Established efficacy:** cornerstone of hemophilia treatment for decades, with a well-understood safety and efficacy profile. Can be used for both prophylaxis and on-demand treatment: Effective for preventing bleeds and for stopping active bleeds.	**Reduced treatment burden:** Subcutaneous administration and less frequent dosing significantly improve convenience and quality of life for patients. Effective in patients with inhibitors to traditional factor replacement, offering a crucial alternative. **Novel mechanisms:** Offers new ways to achieve bleeding control, potentially leading to better outcomes for some patients.
CONS	**Intravenous administration:** Requires regular intravenous infusions, which can be burdensome for patients, especially children. Short half-life (for SHL): Requires frequent infusions to maintain protective factor levels. **Inhibitor development:** Some patients, particularly those with severe hemophilia, can develop antibodies against the infused factor, rendering the replacement therapy ineffective.	**Not suitable for acute bleeds:** designed for prophylaxis and may not be effective for immediately stopping active bleeding episodes. Patients may still need clotting factor replacement. **Newer therapies, less long-term data:** As these therapies are newer, long-term safety and efficacy data are still accumulating compared to decades of experience with replacement therapy.

Gene therapy

Hemophilia is an ideal candidate for GT, being a monogenic disorder with a clearly defined phenotype and a wide therapeutic window. GT offers a potential cure that would provide optimal outcomes while alleviating the burden of treatment with a safe, one-time administration achieving predictable and durable levels of FVIII or FIX to prevent bleeding and the need for chronic treatments. GT involves the use of adeno-associated viruses (AAVs) as vectors to deliver the therapeutic *FVIII* or *FIX* gene to hepatocytes as target cells.

The first successful results for HB were published in 2011. Ten patients with severe HB showed a dose-dependent expression of the FIX transgene of 2-11 IU/dL [29], which was maintained at 2-5 IU/dL after > 10 years. An important advance in GT for HB came with the introduction of the Padua variant of the *FIX* gene, which resulted in R338L amino acid change. This naturally occurring variant, originally reported in a family with inherited thrombophilia, produces a highly active form of FIX, with 5-8-fold enhanced activity compared with the wild-type FIX. In a phase-3 trial, 54 patients with severe HB were treated, achieving mean FIX activity of 39 IU/dL at six months and 36 IU/dL at 36 months [30].

The development of an agent for HA GT has proved to be an additional challenge. Whereas hepatocytes are the physiological site of FIX synthesis, the sinusoidal endothelial cells are the main site of FVIII synthesis in the liver. The first successful results in HA were published in 2017 [31]. Six out of seven treated patients showed sustained normalization of FVIII activity over a period of one year (mean, 93 IU/dL ± 48), leading to stabilization of hemostasis as well as a comparatively sharp reduction in annual factor VIII use. Subsequent declining expression of FVIII over a period of up to six years was demonstrated [32].

A common GT side effect is increased liver enzymes, due to an unpredictable T cell-induced immune response to transduced hepatocytes [33], with possible reduction or loss of therapeutic effect. This occurs more frequently in HA (89%) [34] than in HB (17%) [30]. In 2022, the European Medicines Agency (EMA) granted conditional marketing authorization to valoctocogene roxaparvovec (AAV5-hFVIII-SQ), an AAV5 GT to treat HA, and the US Food and Drug Administration approved etranacogene dezaparvovec-drlb (AAV5-FIX Padua) to treat HB; this was also granted conditional marketing authorization by the EMA in early 2023.

Conclusion

Current treatments for hemophilia allow more effective prophylaxis regimens, reducing bleeding events and making it possible for patients to lead more active and independent lives with an overall improvement in QoL.

With better management of the disease, life expectancy

has also significantly increased, becoming closer to that of the general population. The next ambitious goals can therefore be identified as ensuring a hemophilia free-mind [35] and offering a potential cure through GT.

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