Haemophilia Treatment in 2025

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Abstract
Haemophilia is a rare disease with high morbidity and mortality in its severe form. The mainstay of haemophilia management has been regular prophylactic infusions of the missing coagulation factor (FVIII/FIX) to reduce morbidity and mortality associated with chronic, crippling arthropathy. This approach is burdensome and costly for patients due to the need for frequent intravenous infusions, high costs, limited availability, and the development of inhibitors. Advances in the engineering and manufacturing of clotting concentrates have led to the creation of novel molecules that address many of these limitations. These include the development of extended half-life factors, which require less frequent infusions, and new non-factor replacement treatments that can be administered subcutaneously and infrequently, such as FVIII-mimetic antibodies (e.g., emicizumab) and downregulators of natural anticoagulants (e.g., antithrombin, tissue factor pathway inhibitor, or activated protein C). Finally, gene therapy is set to offer patients the possibility of a cure by transferring a functional copy of the gene required to express the missing or dysfunctional clotting factor. This therapy was approved for the treatment of haemophilia A and B in 2022 in Europe and the United States and is currently in late-phase clinical investigation.

Introduction
The most prevalent X-linked inherited bleeding disorders are haemophilia A and B, characterized by a deficiency or absence of clotting factors VIII (haemophilia A - HA) and IX (haemophilia B - HB), respectively. The severity of the disease is determined by the residual amount of FVIII or FIX, which can be classified as severe (<1%), moderate (1–5%) or mild (6-49%) (1).

Haemophilia A and B share similar symptoms, including bleeding into large joints such as the elbows, knees, and ankles (referred to as index joints). This bleeding can lead to painful and disabling haemophilic arthropathy. Regardless of the severity, life-threatening bleeding, such as intracranial haemorrhages or internal organ bleeding may occur, albeit more frequently in severe cases. While spontaneous bleeding is common in severe haemophilia, those with moderate or mild forms may also experience significant bleeding due to trauma or surgery. Inadequate management can result in chronic disease and lifelong disability (2,3). Fortunately, therapeutic advances and comprehensive care have significantly improved morbidity and mortality in the 21st century.

Treatment
Haemophilia management includes on-demand treatment for bleeding episodes and perioperative management, as well as regular prophylactic treatment designed to reduce bleeding frequency, morbidity, and mortality, thereby enhancing quality of life. Treatment options encompass factor replacement therapy, non-replacement therapies, inhibition of natural anticoagulant pathways that promote thrombin generation, and gene therapies that enable endogenous production of clotting factors. These therapies differ in their approach to prophylaxis and on-demand treatment, method and frequency of administration, duration of effect, level of haemostatic protection, and side effect profiles. Annual bleeding rates and joint damage are crucial markers for evaluating prophylactic treatment efficacy. Personalized management strategies aligned with individual goals, such as participating in competitive sports, should begin at diagnosis and continue throughout life. A multidisciplinary team is essential to support these strategies and provide education to both clinicians and patients (2-4).

Over the past three decades, prophylaxis has become the evidence-based standard of care, proven to better preserve joint integrity than on-demand therapy, especially in patients with severe haemophilia (5,6). The wide availability of recombinant clotting factor concentrates - manufactured using ultrafiltration and nanofiltration viral inactivation techniques and free from animal or human proteins - has facilitated widespread implementation of prophylaxis, at least in high-income countries. However, despite the significant benefits of primary prophylaxis, frequent intravenous injections due to the short half-life of standard half-life (SHL) factor VIII (10–12 hours) and IX (18–20 hours) pose adherence challenges, especially for younger patients. This often necessitates the use of ports or other central venous access devices (3,4,7).

To address these limitations, extended half-life (EHL) recombinant FVIII/FIX concentrates were developed between 2010 and 2020. Techniques include fusing clotting factors with proteins like the Fc domain of IgG1 or albumin, or pegylation using polyethylene glycol (PEG). While FIX modifications yielded a fivefold increase in half-life, results for FVIII were more modest (1.5–1.7x increase). EHL-FIX can allow weekly or every two weeks dosing while maintaining trough levels above 5%, effectively converting a severe phenotype to a mild one. EHL-FVIII's impact is less obvious, typically enables twice-weekly dosing, instead of three times weekly, maintaining trough levels of 2% - 3% thereby transforming severe bleeding into a moderately severe bleeding phenotype. Thus, by reducing the number of venipunctures, prophylaxis became more feasible as the standard, particularly for patients with HB. The EHL factors are satisfactory in terms of safety. Their safety profiles in clinical trials have been consistent with SHL products. No concerns were raised about the high degree of engineering of the molecules, resulting in neoantigenicity and more inhibitors (3,7,8).

Despite these advancements, development of inhibitory antibodies against FVIII/FIX remains a major challenge. Around 30% of individuals with severe haemophilia A and 10% with severe haemophilia B develop inhibitors that neutralize replacement

therapy, limiting prophylaxis options and increasing morbidity and mortality. Bypassing agents (BPAs), such as recombinant activated factor VII (rFVIIa, NovoSeven) and activated prothrombin complex concentrate (FEIBA), were game-changers in the 1990s, but unmet needs, especially regarding injection frequency and practicality, persisted (3-5).

Innovative non-factor therapies (NFTs) emerged between 2010 and 2020. These drugs enhance thrombin generation (e.g., emicizumab, MIM8) or inhibit natural anticoagulant pathways (e.g., fitusiran, concizumab, and marstacimab). Fitusiran, a monthly subcutaneous siRNA therapy, reduces antithrombin levels to restore haemostasis in both HA and HB, with or without inhibitors. Concizumab, an anti-tissue factor pathway inhibitor (TFPI) monoclonal antibody, and marstacimab, a TFPI neutralizing antibody approved in 2024–2025, are administered subcutaneously and aim to reduce bleeding frequency by counteracting TFPI. SerpinPC, another agent under development, targets activated protein C to support thrombin generation in the absence of FVIII or FIX (3-8).

Currently, emicizumab is the only widely used NFT for prophylaxis in HA. This bispecific monoclonal antibody mimics FVIII by bridging FIXa and FX and is administered subcutaneously every 7, 14, or 28 days. Data from the HAVEN 1–4 and HAVEN 7 trials support its use across all age groups, with or without inhibitors. However, emicizumab does not normalize haemostasis, so FVIII or BPAs remain necessary for bleeding or surgery. Breakthrough bleeds still occur, though less frequently (9,10). Emicizumab is not effective for HB.

According to the 2020 WFH guidelines, clinicians aimed for FVIII trough levels >3% - 5% (2). Evidence increasingly supports targeting levels >5%, or even 15%–50%, to achieve near-zero joint bleeding (11). Efanesoctocog alfa, a next-generation FVIII therapy, surpasses the VWF half-life ceiling and maintains FVIII levels well above traditional products. The unique structure of efanesoctocog alfa allows for independent operation of endogenous VWF, resulting in a significantly longer half-life compared to standard and EHL FVIII products. When given prophylactically at 50 IU/kg intravenously weekly, FVIII activity levels increased to 100 – 120% and remained above 40% to day 4 and then were 13–15% at day 7 post infusion in adolescents and adults. Following infusion in children <6 years of age, the time to 40 IU/dL was 59.2 hours and for the 6 to <12 -year-old, 72.2 hours compared to 81.7 hours and 97 hours for the 12 to < 18 and ≥18 -year-old, respectively. In other words, efanesoctocog alfa is a new type of FVIII replacement with an extended half-life also called ultra-extended product, which allows for once weekly dosing to achieve haemostasis and FVIII trough levels of 13-15 IU/dL. This provides a highly effective option for prevention of bleeding in haemophilia A. It also provides a better option for treatment of bleeding and coverage for surgery with fewer infusions (12.13).

Despite these improvements, regular injections and breakthrough bleeds still limit quality of life. Gene therapy offers a potential cure. In 2022, the EMA conditionally approved valoctocogene roxaparvovec (AAV5-hFVIII-SQ) for HA, while the FDA approved etranacogene dezaparvovec-drlb (AAV5-FIX Padua) for HB. However, variability of factor expression level and durability of response are concerns. Median FVIII activity after valoctocogene roxaparvovec declined from 22.9 IU/dL in year 1 to 8.3 IU/dL in year 3. In contrast, FIX levels remained stable at around 37% for three years post-etranacogene dezaparvovec (14-17).

Conclusion

Maintaining FVIII/FIX levels within the normal range is ideal but still difficult. SHL and EHL therapies have long used trough levels as markers of efficacy. However, new findings suggest that time spent above protective thresholds may be more relevant than simply reaching a minimum trough. Non-factor therapies and gene therapy present opportunities to elevate and maintain coagulation activity more effectively and with fewer injections.

Thanks to EHL products and non-replacement therapies, we are shifting from managing severe disease to aiming for a mild—or even non-haemophilia—phenotype. The therapeutic goal is now evolving toward achieving zero bleeds. Gene therapy may be the ultimate step in this evolution. However, due to variability in response and durability, close clinical monitoring remains essential to avoid unrecognized disease activity.

There is no doubt that gene therapy and other innovative treatments will continue to evolve. The future of haemophilia care is bright, with real potential for patients to become haemophilia-free.

Statement

The authors have no conflicts of interest relating to the topic discussed in this manuscript.

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