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REVIEW

Current factor IX replacement options for hemophilia B and the challenges ahead

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ABSTRACT

Introduction: Therapy for hemophilia B is aimed at replacing the congenital deficiency of coagulation factor IX (FIX). For replacement therapy, several FIX concentrates derived from donated human plasma or engineered by recombinant DNA technology are currently commercially available. The use of these products is well established and permit patients a relatively normal life. To further improve treatment efficacy, recombinant FIX products with a prolonged half-life have been developed, allowing relaxed prophylactic dosing and reducing treatment burden.

Areas covered: In this review, we explore the current FIX replacement options for hemophilia B patients by analyzing the outcomes of their main clinical trials. We cover advances in the FIX molecules with extended half-life (EHL). Published literature on products for replacement of hemophilia B was retrieved using PubMed with no temporal limits.

Expert Opinion: The recent introduction of recombinant EHL FIX products has represented a major advance in the therapeutic management of hemophilia B patients, permitting both a reduction of treatment burden and improving patients' compliance to prophylaxis and, ultimately, quality of life.

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Hemophilia B; FIX concentrates; replacement therapy; extended half-life; prophylaxis

1. Introduction

Hemophilia B (HB) is a recessive congenital bleeding disorder with X-linked inheritancy, causing a functional deficit of factor IX (FIX), a serine protease that plays a key role in the coagulation intrinsic pathway [1,2]. HB has an estimated prevalence of 0.5 cases per 10,000 males [3–5]. Historically, one of the most famous HB carriers was Queen Victoria of the United Kingdom, who transmitted the mutated gene to many European courts across Russia, Germany and Spain: for such reason this rare inherited bleeding disorder is called 'royal disease' [6,7].

The molecular basis of HB involves de novo (approximately 30% of cases) or inherited mutations in the *F9* gene. The gene is in the long arm of the X chromosome and the trait is recessive: as such, hemophilia affects almost exclusively males, although approximately 10% of carrier females have mild presentations. *F9* mutations are heterogeneous, with a predominance of missense single nucleotide polymorphism, as reported in the European Association for Hemophilia and Allied Disorders (EAHAD) variant database [8,9].

The severity of hemorrhagic manifestations is related to the residual levels of FIX coagulation (<1% in severe forms; 1–5% in moderate forms; 5–40% in mild forms) [3]. In mild subjects bleeding occurs almost exclusively after major surgery or traumas, with spontaneous hemorrhages being rare. Moderate forms instead are characterized by bleeding after minor trauma, and patients with severe forms suffer frequently from spontaneous bleedings [8]. Indeed, severe HB manifests recurrent joint bleeds and hematomas which, over time, cause severe arthropathy, leading to chronic pain and disability. HB patients experience less severe and less frequent bleedings and a lower likelihood of joint arthropathy than hemophilia A patients with the same level of coagulation factor deficiency [10–13].

This narrative review summarizes the current concepts of replacement therapy in HB, focusing on recent long-acting FIX products currently in phase III development and beyond. Literature search included clinical studies and reviews concerning HB therapy published in PubMed with no temporal limits and using English as language restriction. The Medical Subject Headings (MeSH) terms used for the search were: 'hemophilia B,' 'FIX deficiency,' 'therapy,' 'recombinant FIX therapy,' 'recombinant FIX fusion protein,' 'standard half-life,' 'long-acting' and 'extended half-life.' We also screened the reference lists of the most relevant review articles for further studies not captured in our initial literature search. The results of the literature search are summarized in supplementary Figure 1. Gene therapy for HB, non-replacement therapies, and therapies for the management of HB patients with inhibitors will not be covered in this review.

2. The evolution of hemophilia B therapy

Prompt management of hemophilia is essential to avoid bleeding and long-term complications; thus, scheduled prophylactic regimens to reduce the frequency of bleeding and associated on-demand therapies are the mainstays of hemophilia treatment across the world [14,15]. Today, several FIX products are

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Article highlights

- Hemophilia B is a rare inherited bleeding disorder characterized by deficiency of the coagulation FIX.
- In hemophilia B patients, the clinical severity of bleeding tendency is related to the degree of FIX defect.
- The mainstay of treatment of hemophilia B is replacement therapy with FIX concentrates.
- Several FIX concentrates are currently available, from plasma-derived to recombinant FIX products with standard (SHL) or extended half-life (EHL).
- EHL recombinant FIX products currently represent the best therapeutic approach for hemophilia B, improving patients' adherence to prophylaxis regimens and, ultimately, their quality of life.

authorized for the treatment of HB: plasma-derived products have standard half-life (SHL), while products of recombinant origin can have either SHL or extended half-life (EHL) [16–19]. Table 1 reports the main features of FIX products.

The history of HB therapy starts in the early 1970s with the availability of prothrombin complex concentrates (PCCs) that improved the quality of life, enabling early treatment of hemorrhage, prevention of hemophilic arthropathy and performance of elective orthopedic surgeries to correct or minimize it [20,21]. Unfortunately, the hemophilia community was plagued by the contamination of plasma-derived factor products with HIV, HBV and HCV in the 1980s: it has been estimated that approximately 70% of patients with severe hemophilia got HIV and almost 100% HCV [3]. This tragedy fueled the research for safer plasma-derived products made using viral inactivation strategies such as heat inactivation, pasteurization, and solvent/detergent treatment [3]. Therefore, at the beginning of 1990s, PCCs were replaced by safer (in terms of viral transmission and thrombotic risk) high-purity plasma-derived FIX concentrates [7]. In addition, the cloning of *F9* in 1982 paved the way to the synthesis of new recombinant FIX (rFIX) products, which were marketed in 1997. This revolutionary technology created a platform by which additional bioengineering innovations could further evolve factor replacement therapy, until the recent EHL products [22–25].

3. Extended half-life recombinant FIX products

Several bioengineering strategies have been developed to prolong the half-life of rFIX products. These technologies, aimed at prolonging the time in the circulation of FIX molecule by reducing its degradation and elimination, include fusion to the Fc portion of the IgG, albumin fusion and conjugation to polyethylene glycol (PEG, glycoPEGylation). The effects of PEGylation and protein fusion on the half-life of FIX products are 2–5-fold higher than for current EHL FVIII products, extending dosing intervals up to every other week. Dosing regimens are tailored and adjusted on an individual basis, guided by pharmacokinetic (PK) profile, physical activity, and clinical observation [26,27]. EHL-FIX products can reduce the annual number of infusions needed for prophylaxis by approximately 60%. In this section we report the main characteristics and the clinical trials of the three commercially available EHL FIX products.

3.1. Eftrenonacog alfa

Eftrenonacog alfa (Alprolix, Sobi/Sanofi) is a recombinant protein formed by the fusion of the carboxy-terminus of FIX molecule with the N-terminus of a human IgG_1 Fc monomer. FIX activation is obtained without the need for a cleavable linker between FIX and Fc [28]. A phase I/II clinical trial showed that rFIX-Fc was well-tolerated with a 3-fold longer half-life than native rFIX, with dose-proportional increases in plasma FIX activity [29]. The phase III B-LONG was an open-label, multicenter, non-randomized clinical trial which evaluated PK, safety, and efficacy of rFIX-Fc in 123 previously treated patients (PTPs) with moderate/severe HB aged $\geq$ 12 years [30]. The terminal half-life of rFIX-Fc was 82 hours, approximately 4-fold longer than rFIX, with a median annualized bleeding rates (ABR) in the weekly prophylaxis arm (group 1: starting dose 50 IU/kg) of 3.0 versus 1.4 in the individualized prophylaxis arm (group 2: starting with doses of 100 IU/kg every 10 days) and 17.7 in the on-demand arm (group 3). In group 2, the overall median dosing interval for prophylaxis was 12.5 days and 54% of patients who were recruited in study for $\geq$ 6 months achieved a dosing interval $\geq$ 14 days. Overall, 90% of bleeds were controlled with a single injection of rFIX-Fc, and no drug-related serious adverse events were recorded, including the development of anti-FIX neutralizing antibodies. Finally, hemostasis was rated as excellent or good during all 14 major surgeries (group 4) performed during the study period [30].

The phase III open-label Kids B-LONG trial evaluated rFIX-Fc in 30 PTPs under 12 years old with moderate/severe HB [31]. Children received prophylaxis at a starting dose of 50–60 IU/kg rFIX-Fc, then adjusted on PK results. The median prophylactic dose was 58.6 IU/kg rFIX-Fc given once weekly. Median ABR was 2.0 for all bleeds and 0.0 for spontaneous joint bleeds [31]. No cases of inhibitors occurred.

The long-term (up to 5 years) safety and efficacy of rFIX-Fc were confirmed in the frame of the extension B-YOND trial [32]. The study included 93 subjects from B-LONG and 23 subjects coming from Kids B-LONG studies [32].

The phase III open-label previously untreated patients (PUPs) B-LONG study evaluated the safety and efficacy of rFIX-Fc in 33 pediatric (age<18 years) HB patients [33]. The median ABR for the 28 patients on prophylaxis was 1.2. One patient (3%) developed a low-titer inhibitor. Table 2 reports the main results of phase III trials on eftrenonacog alfa. Finally, a recent study conducted in Ireland in 23 severe HB patients and investigating patient-reported outcomes and health-related quality of life (HRQoL) demonstrated a reduction in chronic pain and improvement in activities of daily living after switching to rFIX-Fc [34].

3.2. Albutrepenonacog alfa

Albutrepenonacog alfa (Idelvion, CSL Behring) is a single-chain protein produced by the fusion of human rFIX with human recombinant albumin (rFIX-FP) connected by a proteolytically cleavable linker, which is cleaved during the activation process to release activated rFIX only [35]. Thanks to the protective effect from degradation of albumin, rIX-FP has an increased circulating half-

Table 1. Characteristics of licensed plasma-derived and recombinant FIX concentrates.

Product	Manufacturer	Origin	Plasma half-life (hours)	Preparation		Notes
				Fractionation	Viral inactivation	
IXED	Kedrion	PD	24	Ion exchange and heparin affinity chromatography, filtration	Solvent/detergent + dry heat (100°C, 30 min)	Specific activity: 100 UI/mg protein
AlphaNine	Grifols	PD	18	Ion exchange and dual polysaccharide ligand chromatography	Solvent/detergent + nanofiltration	Specific activity: >210 UI/mg protein
Immunine	Takeda	PD	24	Ion exchange and hydrophobic interaction chromatography	Detergent + vapor heat (60°C, hrs, then 80°C, 1 hr)	Specific activity: >200 UI/mg protein
Octanine F	Octapharma	PD	35	Ion exchange and affinity chromatography	Solvent/detergent + nanofiltration	Specific activity: >100 UI/mg protein
BeneFIX	Pfizer	R-SHL	16–19	Anionic + metal chelate affinity chromatography	Nanofiltration	Nonacog alfa
Rixubis	Shire	R-SHL	23–26	Ion exchange chromatography	Solvent/detergent + nanofiltration	Nonacog gamma
Ixinity	Emergent BioSolutions	R-SHL	24	Ion exchange chromatography	Solvent/detergent + nanofiltration	Trenacog alfa
Alprolix	Sobi/Sanofi	R-EHL	82	Multistep chromatography	Solvent/detergent + nanofiltration	Eftrenonacog alfa, Fc fusion to rFIX, HEK
Idelvion	CSL Behring	R-EHL	101	Chromatography	Solvent/detergent + nanofiltration	Albutrepenonacog alfa, fusion of rFIX with albumin, CHO
Refixia/ Rebinyn	Novo Nordisk	R-EHL	93	Multistep chromatography	Solvent/detergent + nanofiltration	Nonacog beta pegol, GlycoPEGylated to rFIX, CHO

Abbreviations: PD, plasma-derived; R: recombinant; SHL, standard half-life; EHL, extended half-life; FIX, factor IX; HEK, human embryonic kidney cells; CHO, Chinese hamster ovary cells.

Table 2. Main results of phase III trials with eftrenonacog alfa.

Study [ref.]	NCT number	Study design	Patients (age)	Main results
B-LONG [30]	NCT01027364	Nonrandomized open label study. Pivotal trial.	123 PTP (≥ 12 years)	The median ABR in groups 1 (weekly dose-adjusted prophylaxis with starting dose of 50 IU/kg), 2 (interval-adjusted prophylaxis with starting dose of 100 IU/kg every 10 days), and 3 (on-demand) were 3.0, 1.4, and 17.7, respectively. In groups 1, 2 and 3, 90% of bleeding episodes resolved after one rFIX-Fc injection. No inhibitors were detected. Hemostasis was rated as excellent or good during all major surgeries (group 4).
Kids B-LONG [31]	NCT01440946	Nonrandomized open label study	30 PTP (< 12 years)	The median ABR was 2.0 overall and 0.0 for spontaneous joints bleeds. Ten (33%) of 30 patients reported no bleeding and 19 (63%) reported no joint bleeding on-study. No patients developed inhibitors to rFIX-Fc.
B-YOND [32]	NCT01425723	Nonrandomized open label extension study	93 from B-LONG, 27 from Kids B-LONG	The extension study (up to 5 years) of B-LONG and Kids B-LONG trials confirmed the long-term safety and efficacy of rFIX-Fc treatment.
PUPs B-LONG [33]	NCT02234310	Nonrandomized open label study	33 PUPs (< 18 years)	The median ABR was 1.2 in the 28 patients receiving prophylaxis. One patient (3%) developed a low-titer inhibitor.

Abbreviations: PTP, previously treated patients; ABR, annualized bleeding rates; PUPs, previously untreated patients.

Table 3. Main results of phase III trials with albutrepenonacog alfa.

Study [ref.]	NCT number	Study design	Patients (age)	Main results
PROLONG-9FP [40]	NCT0101496274	Nonrandomized open label study. Pivotal trial	63 PTP (≥ 12 years)	The median ABR in group 1 (prophylaxis once every 7 days for 26 weeks, followed by either 7-, 10, or 14-day prophylaxis regimen) and group 2 (on-demand treatment for 26 weeks, then switched to a 7-day prophylaxis regimen) was 0. Overall, 99% of bleeding episodes were treated successfully and no inhibitor developed.
PROLONG-9FP Pediatric [41]	NCT01662531	Nonrandomized open label study	27 PTP (< 12 years)	The median ABR in children receiving prophylaxis with 35–50 IU/kg once weekly was 0. Overall, 97% of bleeding episodes were treated successfully and no inhibitor developed.
PROLONG-9FP ES [43]	NCT02053792	Nonrandomized open label extension study	59 PTP (≥ 12 years)	The extension study (up to 4 years) of PROLONG-9FP demonstrated a comparable efficacy for both the 14- and 21-day regimens compared to the 7-day regimen. Overall, 96.5% of bleeding episodes were treated successfully with one or two injections of rFIX-FP. No safety issues were reported.
PROLONG-9FP Pediatric ES [44]	NCT02053792	Nonrandomized open label extension study	24 PTP (< 12 years)	The extension study (3 years) of pediatric PROLONG-9FP demonstrated a comparable safety and efficacy for the 7- and 14-day regimens. Overall, 96% of bleeding episodes were treated successfully with one or two injections of rFIX-FP.

Abbreviations: PTP, previously treated patients; ABR, annualized bleeding rates; ES, extension study.

life as compared with standard FIX recombinant and plasma-derived products (90–102 hours versus 18–24 hours), as observed in preclinical and phase I/II clinical studies [36–39].

The phase III PROLONG-9FP was a non-randomized clinical trial in 63 adolescent and adult PTPs (aged 12–61 years) with moderate-to-severe HB [40]. The study included 2 groups: group 1 (prophylaxis) received weekly 35–50 IU/kg rIX-FP for 26 weeks, and eventually switched to 10- or 14-day prophylaxis with 50 or 75 IU/kg rIX-FP, respectively. Group 2 received on-demand treatment during the first 26 weeks followed by 7-day prophylaxis. The mean terminal half-life of rIX-FP was 102 hours, 4.3-fold longer than that of SHL FIX products previously used by patients [40]. In patients who switched from an on-demand to a prophylaxis regimen, a 100% recovery rate of arthropathies was reported and the median spontaneous ABR was 0 [40]. Overall, the great majority (94%) of hemorrhages were successfully managed with a single dose. No inhibitor development was detected.

A phase III trial evaluated PK, safety and efficacy of rIX-FP in 27 PTPs (<12 years) with moderate/severe HB [41]. All children received prophylaxis with weekly 35–50 IU/kg rIX-FP (median prophylactic dose: 46 IU/kg). Again, the mean half-life of rIX-FP was 4.3-fold longer (91.4 hours) than previous FIX product. The median ABR was 0 and 90% of bleeding episodes resolved with one injection and no patient developed inhibitors against FIX [41].

rIX-FP was evaluated in 21 major and minor surgeries performed in 19 patients from the two previous phase III trials [42]. Hemostatic efficacy was excellent or good for all procedures, and a single pre-operative rIX-FP dose maintained intraoperative hemostasis in almost all (20/21) surgeries.

In the 4-year phase III extension study, adults and adolescents with controlled HB under treatment with rIX-FP every 2 weeks switched to every 3 weeks schedule (100 IU/kg) [43]. The mean trough FIX activity levels were 22, 14, and 7.6% in patients on 7-, 14- and 21-day prophylaxis at median doses of approximately 50, 75, and 100 IU/kg, respectively. Median ABR were 0, 0.3, 0.4 and 0 for the 7-, 10-, 14-, and 21-day regimens, respectively. Comparable efficacy was shown for both the 14-, and 21-day regimens compared to the 7-day regimen. No patients developed inhibitors.

In the long-term (3 years) phase III extension study in children receiving rIX-FP 50–75 IU/kg every 14 days, a mean steady-state trough FIX level of 7.2% was maintained [44]. The 7- and 14-day regimens were comparable in preventing spontaneous hemorrhages. No patients developed inhibitor. Table 3 reports the main results of the phase 3 trials on albutrepenonacog alfa.

3.3. Nonacog beta pegol

Nonacog beta pegol (N9-GP, Refixia/Rebinyn, Novo Nordisk) is a rFIX molecule produced by site-directed glycoPEGylation (40 kDa). When FIX is activated, the activation peptide and the attached PEG moiety are cleaved, thus leaving the wild-type activated FIX which has a prolonged half-life *in vivo* [45]. A set of phase III clinical trials (named Paradigm) have assessed the safety and efficacy of N9-GP [46].

Paradigm 1 phase I trial investigated 16 HB PTPs who received one dose of their usual FIX product followed by the same dose of N9-GP: a 5-fold extension of the half-life (mean 93 hours) was achieved, allowing for once-weekly prophylaxis [47].

The phase III trial (Paradigm 2) on 74 adult and adolescent PTPs with moderate/severe HB was a single-blind randomized clinical trial (RCT) aimed at investigating PK, safety, and efficacy of N9-GP [48]. Patients received either episodic or prophylactic treatment and those on prophylaxis were randomized to receive either 10 IU/kg or 40 IU/kg N9-GP once weekly for 52 weeks [48]. The median ABR were 2.9, 1.0 and 15.6 in the 10 IU/kg, 40 IU/kg and on-demand treatment arm, respectively. In the 40 IU/kg prophylaxis group, 67% of patients experienced no bleeding episodes into target joints compared with only 7.7% of patients in the 10 IU/kg group. No patients developed inhibitors [48].

Paradigm 3 evaluated efficacy and safety of N9-GP in the peri- and post-surgery period across 13 major surgeries in 13 patients [49]. All patients received a pre-operative bolus of 80 IU/kg N9-GP followed by fixed doses of 40 IU/kg repeated according to investigator's indication. Intra-surgery efficacy was rated excellent or good in all 13 cases. The median number of post-surgery doses was 2.0 on days 1–6 and 1.5 on days 7–13 with a total median consumption of 126.1 IU/kg over two weeks. No severe adverse events, including inhibitor development, were observed [49].

The 71 patients who completed either the Paradigm 2 or Paradigm 3 trials were eligible for enrollment in an open-label,

Table 4. Main results of phase III trials with nonacog beta pegol.

Study [ref.]	NCT number	Study design	Patients (age)	Main results
Paradigm 2 [48]	NCT01333111	Randomized single-blind study. Pivotal trial	74 PTP (≥ 12 years)	The median ABR were 2.9, 1.0 and 15.6 in the 10 IU/kg prophylaxis, 40 IU/kg prophylaxis and on-demand treatment groups, respectively. 67% of patients' in the 40 IU/kg prophylaxis group experienced no bleeding episodes into target joint versus 7.7% of patients in the 10 IU/kg prophylaxis group. No inhibitors occurred.
Paradigm 3 [49]	NCT01386528	Nonrandomized open label study	13 PTP (≥ 12 years)	In this surgery trial, hemostasis after N9-GP infusions was rated excellent or good in all 13 major surgeries. No inhibitor occurred.
Paradigm 4 [50]	NCT1395810	Nonrandomized open label study	71 PTP (≥ 12 years)	In the extension study of Paradigm 2 and 3, a favorable safety profile was shown, with good prophylactic protection (ABR for the 10 IU/kg and 40 IU/kg treatment arms was 1.4 and 1.0, respectively) and control of bleeding (95% success rate) in PTP.
Paradigm 5 [51,52]	NCT01467427	Nonrandomized open label study	25 PTP (≤ 12 years)	The median ABR in the overall pediatric population with once-weekly prophylaxis with 40 IU/kg N9-GP for 50 ED was 1.0. Overall, 86% of bleeds were solved after one single N9-GP injection. No inhibitor developed. These results were confirmed in a 5-year long-term analysis of the study.
Paradigm 6 [53]	NCT02141074	Nonrandomized open label study	37 PUPs (< 6 years)	A 6.1% inhibitor incidence was detected. Efficacy was high (median ABR was 0 and in 94% of bleeds the hemostatic control was rated excellent or good).

Abbreviations: PTP, previously treated patients; ABR, annualized bleeding rates; ED, exposure days.

nonrandomized, multicenter extension trial (Paradigm 4), which investigated the long-term safety and efficacy of N9-PG [50]. The bleed response rate was 95%; most (88%) resolved with one N9-GP injection. The median ABR for patients on prophylaxis was 1.4 and 1.0 for the 10 IU/kg and 40 IU/kg treatment arms, respectively. Hemostatic perioperative outcomes for 23 minor surgical procedures were excellent or good [50]. No patient developed an inhibitor.

A phase III trial investigated safety, efficacy and PK of N9-GP in 25 children with moderate/severe HB (Paradigm 5) [51]. Children were divided into two age groups (0–6 and 7–12 years) and received once-weekly prophylaxis with 40 IU/kg N9-GP for 50 exposure days. The median ABRs were 1.0 in the total population and 86% of bleeding episodes were successfully managed with one N9-GP dose. No patient developed inhibitors and no safety concerns were identified [51]. These positive results (mean ABR 1.0, 93% of bleeding control with 1 to 2 N9-GP injections and no inhibitor occurrence) were confirmed in the 5-year long-term analysis of the study [52].

In the interim analysis of the Paradigm 6 trial, investigating the safety and efficacy of N9-GP in 37 PUPs aged<6 years, an inhibitor incidence of 6.1% was reported [53]. During the prophylaxis phase (40 IU/kg once weekly), most patients (68%) were free from any bleed and the median ABR was 0. Hemostatic efficacy was excellent or good in 94% of bleeding episodes in the overall population [53].

Finally, the Paradigm 7 was a multicenter, open-label RCT which demonstrated favorable pharmacokinetic characteristics of N9-GP versus rFIX-Fc [54]. Table 4 summarizes the main results of phase III clinical studies of nonacog beta pegol.

4. Conclusion

Replacement therapy for HB has greatly evolved over the past 50 years, from plasma-derived to rFIX products. Among the latter, the recent introduction of EHL FIX products has further revolutionized the management of HB patients, improving patients' adherence to prophylaxis regimens and, ultimately, their quality of life.

5. Expert opinion

The goal of HB therapy is the replacement of the deficient coagulation FIX with FIX concentrates, which include plasma-derived and recombinant products and can be administered as prophylaxis (either short or long-term) or on-demand. Long-term prophylaxis is currently considered the standard of care for severe forms [55] but results in increased costs. SHL FIX products require an infusion frequency of at least twice a week to maintain plasma FIX levels above the desired safety level (>1 IU/dl), which negatively impact patients' compliance and clinical outcomes. By modifying the PK properties of rFIX, a new class of FIX products have been recently developed with a 4- to 6-fold prolongation of the FIX half-life [56,57]. The review of the phase III trials in adult and pediatric PTPs shows that EHL rFIX products allow to space injections to every 10 or even 15 days, thereby reducing the number of annual injections by about 50%, compared to SHL FIX products [26]. Thanks to these new agents, trough plasma FIX levels can be kept above 5%, thus transforming a severe phenotype into a mild phenotype. In addition, the possibility of adjusting dose according to an individual's PK data allows a personalized treatment approach, which further reduces patients' bleeding frequency and arthropathy [26]. Although no head-to-head direct comparisons have been performed so far between the different EHL rFIX products, the results of pivotal and extension phase III studies show a comparable high safety and efficacy profile. As these new EHL agents have led to a significant reduction in the infusion number and, ultimately, in the patients' perceived quality of life, they have rapidly replaced the other plasma-derived or SHL rFIX products as the standard of HB care. Such bioengineered products probably represent the best progress of the pharmaceutical research in this field, difficult to further improve. The scenario is much more satisfactory for EHL rFIX than for EHL recombinant FVIII (rFVIII) products because their longer half-life (plasma half-life of 80–100 hours for EHL rFIX versus 14–19 hours for EHL rFVIII products).

Also with EHL rFIX products, however, there are a number of still opened issues, including long-term outcome data on safety, particularly regarding the immunogenicity in previously untreated

patients, and on joint status. EHL rFIX factors have a high safety profile and the initial concern that the high degree of engineering of the molecules might lead to neoantigenicity and more inhibitors does not appear to have materialized. Other concerns regard the potential consequences of lifelong exposure to pegylated products, as emphasized by the fact that European Medicines Agency (EMA) approved pegylated coagulation factors only for subjects aged≥12 years. Finally, the goal of avoiding all intercurrent bleeding episodes and obtaining the magic of zero bleeds, with the consequent effective prevention of the development of arthropathy, seems to be unreachable even with EHL rFIX products. Only long-term and real-world studies, however, will elucidate these still unanswered issues.

The future of the research in HB therapy continues to evolve outside FIX replacement therapy. A number of innovative therapies are currently promising and under clinical development, including non-factor replacement therapies (e.g. fitusiran, serpinPC, concizumab, befovacimab), as well as gene therapy (e.g. Hemgenix™), pursuing the final goal, still unrealized, of zero bleeds in hemophilia patients. The main hurdle is likely to remain the economical sustainability of these high-cost therapies, especially gene therapy. However, if the real-life long-term results of gene therapy for HB confirm that FIX levels attained in plasma after a single infusion are high and sustained enough to prevent at least all spontaneous bleeds and document the safety of such procedure, it is reasonable the HB patients may prefer in the next future this curative approach over replacement and non-replacement therapies.

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