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CLINICAL PRACTICE

The use of rIX-FP in patients with haemophilia B: a nurse's perspective

Kara Garner, Christine Guelcher, Debra Pollard

The management of patients with haemophilia is complex and requires lifelong care to be delivered by a specialist multidisciplinary team. Haemophilia B results from a deficiency or absence in coagulation factor IX (FIX), leading to easy bruising, and musculoskeletal and internal bleeding. For patients with severe or moderate haemophilia B, prophylaxis with standard half-life (SHL) coagulation FIX products requires frequent intravenous administration, which may negatively impact treatment adherence and increase burden of care. A recombinant fusion protein linking recombinant FIX (rFIX) with recombinant human albumin, rIX-FP, has an extended half-life compared with SHL rFIX, and has demonstrated a favourable safety and efficacy profile for the prevention and treatment of bleeding episodes in phase III and real-world studies of patients with severe haemophilia B. rIX-FP enables treatment to be tailored to the needs of individual patients, with dosing flexibility allowing selected patients to be treated with prophylaxis dosing intervals of 7, 10, 14 or 21 days. Patients switching to rIX-FP can reduce their annualised bleeding rate and some have successfully reduced their prophylactic dosing frequency while maintaining low bleeding rates and consistent factor consumption. This may ultimately minimise the occurrence of haemophilic arthropathy and improve patient quality of life. Educating patients and caregivers on the sustained use of rIX-FP prophylaxis is essential. The lifelong support and guidance provided by healthcare professionals at haemophilia treatment centres (HTCs) are critical for providing an optimal treatment approach that can increase adherence to treatment. This article reviews the pharmacokinetics, efficacy, and safety of rIX-FP demonstrated in clinical trials and clinical practice, and discusses haemophilia nurses' clinical experiences with rIX-FP in patients in their HTCs.

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With an extended half-life that enables a flexible dosing regimen, rFIX-FP can benefit haemophilia B patients by offering effective treatment with reduced treatment burden. Nurse specialists have a complex but key role in ensuring that patients and caregivers are well informed, supported and empowered to choose a treatment approach that works best for them.

KARA GARNER
St Luke's Hemophilia Center, Boise, ID, US. Email: karagarner@cableone.net

CHRISTINE GUELCHER
Children's National Hospital, Washington, DC, US

DEBRA POLLARD
Royal Free London NHS Foundation Trust, London, UK

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Haemophilia is a rare bleeding disorder caused by deficiency or absence of coagulation factors VIII (FVIII, haemophilia A) or IX (FIX, haemophilia B) [1]. Although haemophilia B is less common than haemophilia A [2], with approximately 1 in 50,000 individuals being born with haemophilia B, its prevalence is significantly higher than previously thought [3]. The normal range of FIX in plasma in a healthy individual is 50–150 IU/dL; patients with FIX levels <1 IU/dL are considered to have severe haemophilia B, which results in frequent spontaneous bleeding episodes. Patients with FIX levels of 1–5 IU/dL are considered to have moderate disease, and those with levels of >5–40 IU/dL to have mild haemophilia B [1]. Most individuals with haemophilia B are men; however, women may have subnormal amounts of clotting factor, and those with factor levels <40% are also considered to have mild haemophilia. Women can be 'carriers' of haemophilia, with approximately one-third of carrier women experiencing low factor levels that may result in abnormal or prolonged bleeding [4,5]. Those with factor levels of 40–60% of normal that experience abnormal bleeding are known as symptomatic carriers [1].

In addition to bleeding complications, studies have evaluated quality of life in patients with haemophilia, reporting other comorbidities that increase the burden of disease [6,7]. These include treatment burden (with prophylaxis treatment requiring regular intravenous infusions to control and prevent bleeding), absenteeism from school or work, anxiety and depression. Research now focuses on these psychological factors, as well as physical and social aspects.

There is currently no cure for haemophilia; however, several therapies with the potential to significantly decrease treatment burden and increase patient quality of life are currently undergoing clinical testing. Non-factor replacement therapies, while not a curative method, provide the potential for reduced treatment burden and a more efficacious option for patients, particularly those with inhibitors. Preliminary data from gene therapy trials show sustained increases in FIX expression to functionally curative levels 26 weeks following a single treatment [8]. While permanent FIX expression has not yet been established, these results signify the first potential cure for haemophilia B.

The current goals for treating children with haemophilia are early diagnosis and prevention of life-threatening bleeding episodes using prophylaxis. Prophylaxis can reduce the likelihood of spontaneous intracranial haemorrhage, which is associated with significant morbidity and mortality, and can also decrease consequences associated with recurrent musculoskeletal bleeding [1]. Recent haemophilia treatment advances include new recombinant FIX (rFIX) products with improved pharmacokinetic (PK) properties that aim to reduce the burden of prophylaxis [9]. The introduction of extended half-life (EHL) products, designed to have prolonged activity compared with standard half-life (SHL) products, have also enabled less frequent infusions while maintaining high factor levels and protection against spontaneous bleeding [10].

This review aims to inform healthcare professionals on the real-life management of patients with haemophilia B and discuss how treatments have advanced in recent years with the introduction of rFIX products. In particular, this review focuses on the clinical profile of an EHL rFIX product, rIX-FP (a recombinant fusion protein linking recombinant coagulation FIX with recombinant human albumin (IDELVION®, albutrepenonacog alfa, CSL Behring, PA, USA) [11]), and how it can be used to optimally treat patients with haemophilia B.

PRESENTATION AND DIAGNOSIS OF HAEMOPHILIA

Haemophilia B has three classifications: severe, moderate or mild, based on the level of plasma FIX in affected individuals [1]. Severe haemophilia B is associated with spontaneous bleeds that may occur anywhere but are frequently seen in the muscles, soft tissues and major joints [12,13]. Bleeding that occurs in deep muscles or smaller areas can lead to acute compartment syndrome, causing painful swelling that results in increased pressure within a muscle compartment. This may compress nerves and lead to paraesthesia, and reduce capillary perfusion, eventually leading to tissue necrosis. If left untreated, this can have a significant impact on limb function and may cause nerve palsy and permanent disability [14]. Recurrent bleeding into joints leads to crippling arthropathy, and bleeding in the intracranial, neck, throat or gastrointestinal tract may be life-threatening or associated with significant morbidity. In addition, bleeding episodes related to trauma may be more frequent in childhood and adolescence than in adulthood due to increased physical activity levels and a lower ability to determine the risk associated with an activity.

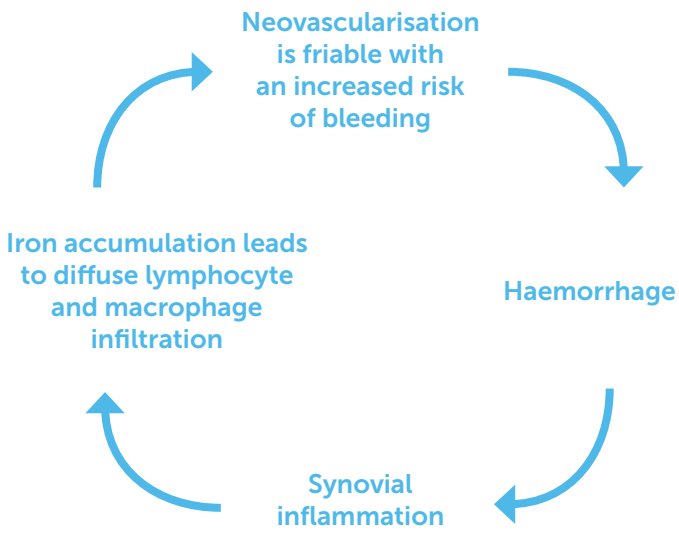
Accurate diagnostic testing is essential for the optimal management of haemophilia B and involves a multifaceted approach, including an evaluation of clinical and family history, a physical examination,

and clotting factor testing [1,15,16]. A bleeding disorder should be considered in a child if they present with any of the following clinical features with or without a family history of haemophilia: prolonged bleeding after circumcision or heel poke, poor wound healing at the umbilical stump, haemarthrosis, haematomas, intracranial bleeding in the absence of major trauma, prolonged oozing, oral or nasal bleeding and/or excessive bruising [1, 15]. Severe haemophilia B is often diagnosed within the first month of life [15]; however, individuals with no family history may not be diagnosed until 1–2 years, once the child is mobile. It is also important to note that while patients with severe/moderate disease (<5 IU/dL) often present with symptoms at a young age, some, including those with mild disease or carrier women, do not present until later in life or until they undergo invasive procedures such as surgery. If a patient is suspected of having a bleeding disorder, factor activity in the blood should be measured; if FIX levels are <40 IU/dL, genetic mutational analysis can confirm a diagnosis of haemophilia B [1].

JOINT BLEEDS

Joint bleeds are the leading cause of chronic pain and disability in people with severe haemophilia. As little as one joint bleed per year has been shown to cause irreversible damage and patients with severe haemophilia not receiving prophylaxis may experience joint bleeds as often as two or three times a month [17,18]. Patients with mild haemophilia may only encounter the problem following trauma. Clinical symptoms are, however, just the tip of the iceberg, and subclinical bleeding can also lead to haemophilic joint arthropathy. The development of haemophilic arthropathy occurs in three stages: acute haemarthrosis, chronic synovitis and degenerative arthritis (Figure 1) [19,20]. Bleeding into joints causes specific changes in the synovium and cartilage, causing pain and inflammation. When bleeding occurs, enzymes from the swollen synovium destroy the cartilage that covers the ends of the bones over time, resulting in cartilage damage and bone erosion. Recurrent joint bleeds eventually lead to a breakdown of the joint lining which causes long term, irreversible joint damage resulting in a painful arthritic condition known as haemophilic arthropathy [1,19-21]. The ankles, knees and elbows, known as index joints, are most susceptible to joint bleeds, but bleeds can also occur in the hips, shoulders, fingers and toes [12]. Joint bleeds rarely occur in the spine, ribs, skull and pelvis because these joints do not have synovial membranes [20].

Figure 1. Process of subclinical bleeding [20]



PEDNET (European Paediatric Network for Haemophilia Management) Group and the Canadian Consensus Definition Group define a target joint as a joint in which at least three or four bleeds have occurred within a 3–6-month period [22,23]. A joint is no longer considered a target joint when there has been no bleeding into it for 12 months.

TREATMENT AND PREVENTION OF BLEEDING EPISODES

Over the past 50 years, the diagnosis and treatment of haemophilia have improved considerably. Currently, treatment for haemophilia B revolves around replacing insufficient FIX in the plasma, using either plasma-derived FIX (pdFIX) or rFIX products [9]. Patients can treat when required during an active bleed (episodic) or using regular intravenous infusions to prevent bleeding (prophylaxis) [1,24]. Episodic treatment is used in patients with mild to moderate disease and prophylaxis treatment is recommended in patients with severe disease or moderate disease with a severe bleeding phenotype [25]. Prophylactic treatment with FIX replacement to prevent bleeding is the standard of care for all patients with severe disease, maintaining FIX activity levels >1 IU/dL at all times. A report by the World Federation of Hemophilia (WFH) suggests maintaining trough levels, e.g., 3–5 IU/dL, to decrease the risk of spontaneous bleeding associated with lower factor levels, as the optimal approach for treating patients with severe haemophilia [1,26]. More recently, personalising the desired trough level to maintain higher activity levels (e.g., >5 IU/dL) has been favoured to reduce the occurrence of spontaneous or subclinical bleeds [1,27].

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Prior to a period where bleeding is more likely (e.g., before a sports game or dental/invasive surgery), a personalised dose can be administered to obtain peak factor levels (normal levels or above) in order to provide the most protection to the patient.

To achieve and maintain higher trough levels, a number of strategies have been applied to improve the PK and pharmacodynamic (PD) properties of FIX, as well as to prolong the duration of action. These include fusion with recombinant proteins such as albumin (rIX-FP, CSL Behring) or the fragment-crystallizable (Fc) section of immunoglobulin G1 (Fc-fusion; rFIXFc, Sanofi Genzyme), and the attachment of a polyethylene glycol (PEG) molecule (PEGylation; N9-GP, Novo Nordisk) [28]. As well as the improved PK properties associated with EHL products, product pricing may be a consideration to switching. A recent economic analysis in the US has shown significantly increased direct costs associated with EHL products compared with SHL products [29]; however, costs and healthcare services vary across regions and countries and this analysis does not include the expected reduced indirect costs associated with more efficacious treatment strategies. Long-term prophylaxis is associated with improved patient outcomes, including reduced pain and joint damage, the major long-term complication of untreated haemophilia, and reduced spontaneous bleeding, and improved overall health and quality of life [30].

Despite the numerous factor replacement products available, treatment is not without its challenges. Patients treated with an SHL rFIX product, with a half-life of 22 hours, typically require 2–3 infusions per week [31]. The frequency of injections creates a burden for both patients and caregivers, which has shown to impact long-term adherence [32]. In the last decade, EHL rFIX products have been developed, with half-lives up to 104 hours [33]. These have been designed to address the burden of disease by enabling some patients to reduce their infusion frequency while maintaining high FIX activity levels and minimising or even abolishing the occurrence of spontaneous bleeding [9,27]. Analysis of patient-level real-world data demonstrates that the use of EHL rFIX products can result in lower mean annualised bleeding rates and higher levels of adherence compared with SHL rFIX products [34].

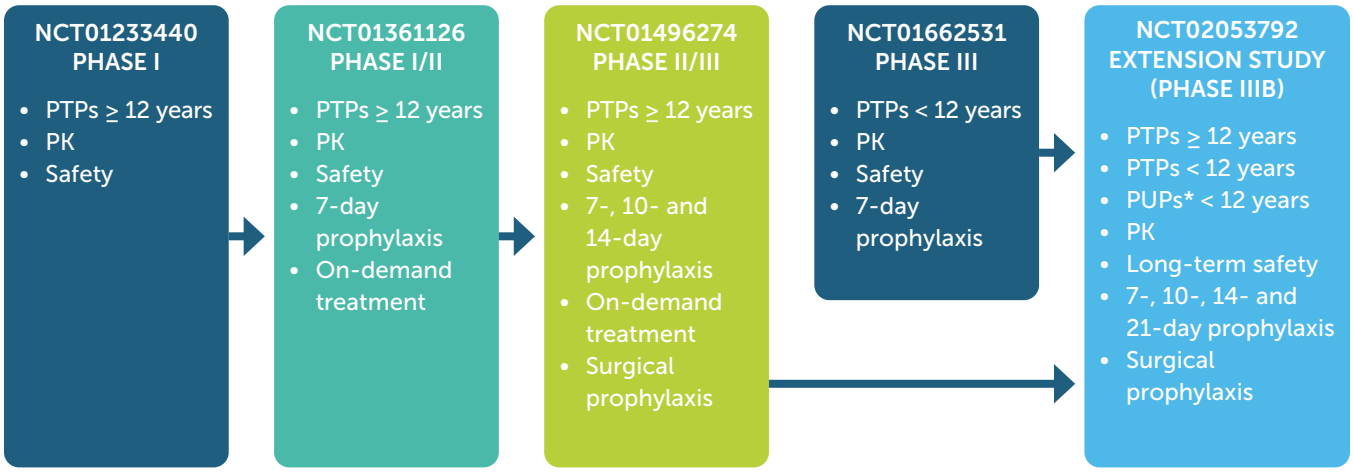
One of the most burdensome complications of factor replacement therapy is the development of inhibitors; however, unlike haemophilia A, only a small proportion of patients with haemophilia B develop inhibitors to FIX (~3% in haemophilia B vs. ~35% against FVIII in haemophilia A [35]) that render FIX replacement therapy ineffective [2,36]. It is important to note that some patients who develop inhibitors suffer from complications such as allergic reactions, nephrotic syndrome, or anaphylaxis following FIX infusions.

THE USE OF rIX-FP IN CLINICAL TRIALS

The clinical development programme for rIX-FP (PROLONG-9FP) was initiated in 2010 to establish the PK, efficacy and safety of rIX-FP in paediatric, adolescent and adult patients. The previously treated patient (PTP) studies have completed, and the previously untreated patient (PUP) study has been halted following new guidance that disease registries should be used to retrieve safety data from this population (Figure 2) [37]. The clinical programme consisted of a phase I dose-finding study [38], phase I/II study in adults and adolescents [39], and three phase III trials. PK data from the early phase studies demonstrated that rIX-FP has an extended circulating half-life, increased area under the FIX activity time curve, lower clearance and an increased incremental recovery compared with standard-acting rFIX (BeneFIX®, nonacog alfa, Pfizer) (Table 1) [11,31]. In the phase III study, adult and adolescent patients (≥12 years) received prophylaxis with 35–50 IU/kg rIX-FP every 7 days or 50–75 IU/kg every 10 or 14 days; paediatric patients (<12 years) received prophylaxis with 35–50 IU/kg rIX-FP every 7 days (Figure 3). Additionally, patients receiving episodic treatment of bleeding episodes for 26 weeks could then be switched to a 7-day prophylaxis regimen. The detailed phase III study design and results of the adult/adolescent [40] and paediatric [41] studies have been described previously; briefly, rIX-FP was shown to have excellent efficacy in the control of spontaneous bleeding episodes and high sustained trough levels in patients of all ages. These findings demonstrate the successful transition of the majority of patients with severe haemophilia to a mild haemophilia phenotype (Table 2) [40,41].

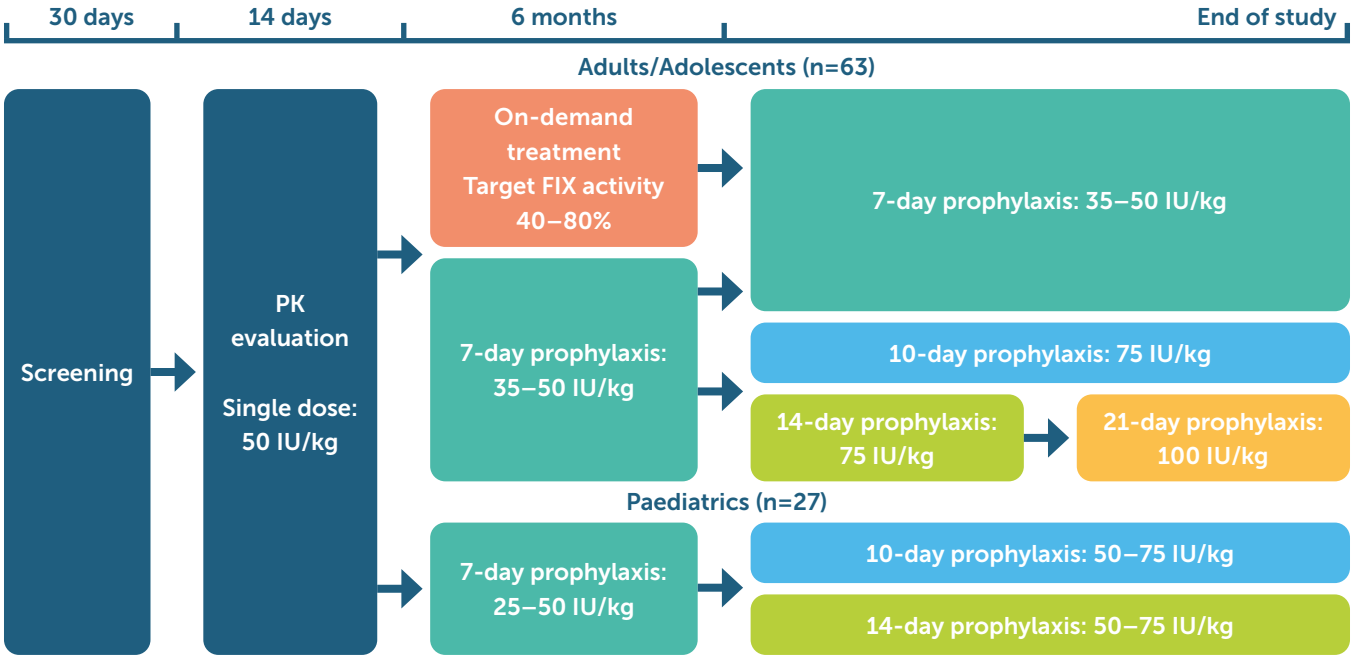
Following this study, patients could enrol in the phase IIIb extension study and further extend their dosing interval if they were well controlled on their current regimen for at least 6 months [42,43]. In addition, 21-day dosing intervals were trialled, whereby adult patients ≥18 years could extend their dosing interval to every 21 days at a dose of 100 IU/kg, if they were well controlled on a 14-day regimen for at least 6 months (Figure 3) [42]. Similarly, paediatric patients could extend their dosing interval to every 14 days at a dose of 50–75 IU/kg, if they were well controlled on a 7-day regimen. The results from this study showed low bleeding rates on all regimens, demonstrating that

Figure 2. PROLONG-9FP clinical trial programme [37]
Figure updated from Santagostino et al., 2016



PK: pharmacokinetics PTP: previously treated patient
PUP: previously untreated patient rIX-FP: recombinant factor IX albumin fusion protein
*PUPs study was halted following guidance that safety data in this population should be gained from disease registries

Figure 3. rIX-FP phase III/IIIb extension study treatment programme in adult/adolescent and paediatric patients



PK: pharmacokinetics rIX-FP: recombinant factor IX albumin fusion protein
*Only patients ≥18 years were able to switch to the 21-day regimen if they were well controlled on the 14-day regimen for at least 6 months

selected patients can be treated with alternative dosing regimens, and no safety concerns were reported [40-43]. Overall, this dosing flexibility enables patients to benefit from a combination of advantages, such as reduced injection frequency and FIX consumption while maintaining low bleeding rates. This may minimise the burden of treatment and increase patient empowerment and independence from physicians, allowing patients to be more in control of their treatment through self-administration and home management [40-43].

In July 2020, the European Medicines Agency (EMA) approved the new Summary of Product Characteristics (SmPC) for IDELVION, which comprises new, extended dosing options, including the possibility of further extension of the treatment interval up to 21-day

Table 1. Pharmacokinetics of rIX-FP compared with rFIX reported in phase III studies [11,31]

	rIX-FP		rFIX	
	50 IU/kg (N=46) [40]	75 IU/kg (N=8) [33]	50 IU/kg (N=11) [31]	75 IU/kg (N=17) [58]
Half-life (hours)	101.7	104	18.1	22.5
Clearance (mL/h/kg)	0.769	0.84	0.84	7.5*
AUC∞ (IU*h/dL)	7176	9345	548	1070
IR (IU/dL)(IU/kg)	1.27	1.08	0.84	0.80

AUC: area under the curve
FP: fusion protein
IR: incremental recovery
rFIX: recombinant FIX
*Parameter from initial pharmacokinetic visit (other values quoted from final visit)

dosing for appropriate adult patients over 18 years. It is essential to note that the 21-day regimen for adults is not approved in the US and the 14-day regimen for paediatrics is currently not approved for use in the EU or US.

This clinical trial programme has demonstrated that rIX-FP effectively replaces the missing coagulation FIX needed for haemostasis, and some patients can successfully extend their dosing interval while maintaining high FIX activity levels [44]. rIX-FP has also been shown to be well tolerated, effectively maintaining haemostasis during and after surgery [45], and paediatric patients treated with rIX-FP prophylaxis have demonstrated improved health-related quality of life [46].

USING rIX-FP IN ROUTINE CLINICAL PRACTICE

The real-world utilisation of rIX-FP in patients with haemophilia B in Germany [47] and in Italy, Belgium and the UK [48] has been reported, demonstrating similar outcomes to the clinical trial experience. These retrospective analyses of patient records found that patients successfully switched from prophylaxis with their prior FIX product to rIX-FP prophylaxis. In some cases, patients were able to reduce their dosing frequency, while maintaining similar bleed protection before and after switching product. In addition, mean factor consumption reduced in patients who switched to rIX-FP from their prior SHL FIX product [47,48].

COMPREHENSIVE CARE APPROACH

The comprehensive care team within a haemophilia treatment centre (HTC) is made up of numerous healthcare practitioners, including physicians, nurses, social workers and physiotherapists [1].

The care provided by nurses is complex. For a patient with severe haemophilia, the primary goal is to prevent pain and discomfort by encouraging patients/caregivers to be compliant with their prophylaxis regimen in order to maintain FIX activity levels >1 IU/dL. Educating patients/caregivers on the role of prophylaxis infusions in bleed prevention and the signs and symptoms of bleeding, and coordinating home infusion, are therefore vital in maintaining optimal physical health, mobility and activity in the patient.

Reducing the burden of disease is also a crucial factor in patient care and finding the optimal treatment throughout the patient's life is essential. To accomplish this, nurses play a crucial role in product choice, incorporating an understanding of therapeutic products and modes of delivery, as well as practical aspects of administration, calculating appropriate doses, and determining the appropriate prophylaxis regimen, ultimately providing personalised care.

Finding the suitable therapeutic product for a patient is complex and often involves a shared decision-making process between HTC staff and the patient/caregiver, taking into consideration the site of the bleed, age of the patient, previous exposure to plasma-derived factors, cost, efficacy, and safety of the products [49]. It is also essential to maintain regular follow-up appointments to ensure the selected therapy's effectiveness and alter the treatment choice, if necessary, in the ever-changing landscape of haemophilia therapy.

The introduction of home therapy has empowered patients and their families to manage haemophilia more independently; however, self-management is demanding and complex. Telephone or video appointments, as well as web-based and mobile apps and social media interventions, have provided a huge advantage for patients and caregivers to manage haemophilia outside of the clinic [50]. This network of support has become particularly important with the changes in clinical practice that have resulted from the COVID-19 pandemic, which has included disruption to patient management through the temporary closure of hospitals to non-COVID-19 patients [51].

Education for all patients and caregivers is important and typically provided by nurses during

follow up appointments, both in clinic and remotely, as well as through formal and informal training. Self-administration programmes can be valuable resources for patients learning how to manage their treatment at home (or outside the HTC) and, importantly, during emergencies. For example, home management of young children with haemophilia, who may be more prone to accidents due to their physical activity levels, is crucial in reducing their impact. Similarly, providing appropriate care for the elderly, who are likely to have received poorer levels of care in early life due to a lack of accessibility and availability of efficacious products, is essential as many among this patient group will have complications related to their bleeding disorder, in addition to the risk of age-related complications seen in the general population. Close coordination between specialties is key to optimising the care of the older haemophilia population as they face additional challenges, such as chronic joint arthropathy which provokes falls and fractures, and complications related to HIV and hepatitis C infection which greatly affect the incidence of cancer and liver disease. Elderly patients with haemophilia may require more assistance to retain their physical and emotional independence; however, beyond the comprehensive managed care plan, there is still a lack of evidence on which to base guidelines on how to treat the older haemophilia population and age-related comorbidities.

PROVIDING A NURSE PRACTITIONER PERSPECTIVE ON THE USE OF rIX-FP IN CLINICAL PRACTICE

The role of each haemophilia nurse practitioner is vital in the management of home-based treatment. Nurses remain the primary point of contact for clinical advice for patients and caregivers, and the importance of maintaining a strong therapeutic relationship cannot be understated [52]. The effect of integrated, comprehensive care on patient-important outcomes in this complex disease have previously been reported, resulting in published guidelines for nurse practitioners to provide the necessary treatments directly to patients in their homes [52,53].

As haemophilia is a lifelong condition, nurse practitioners should be aware of particular challenges that may arise at different life stages, including complications that may result from both treatment and the condition itself. The most critical barrier to treatment is awareness, involving lack of education or retention of information among patients regarding the signs and symptoms of a bleed, as well as importance of early therapy [54]. It is also common for parents/caregivers of school-age children to exhibit inconvenience and scheduling barriers to prophylaxis treatment. As newer products become available, the discussion between healthcare professionals and the patient and/or their caregiver are essential to providing an individualised treatment programme to ensure successful switching between products. Although experience varies between centres, familiarity with a medication and the perception of success in clinical trials are important considerations when deciding on a product.

Patients may have a fear of initiating prophylaxis infusions or changing product, particularly if they feel their current treatment is sufficient [55]. Similarly, patients report not wanting to initiate prophylaxis due to fear of intravenous infusions, poor venous access and the lifelong commitment to treatment, all of which can lead to delays in treatment and impact on compliance, overall treatment success and patient quality of life [56]. Distance to the HTC and access to replacement therapy can also delay treatment for some patients [56,57]. In addition, some patients experience financial barriers related to the cost of therapy and the accessibility of a product influenced by insurance and out-of-pocket expenses [56].

Identifying and managing individual barriers could result in earlier treatment and the prevention of long-term joint damage in paediatric patients, which may also lead to better overall health and quality of life in patients with haemophilia. Importantly, the quality of the relationship between healthcare professionals and the patient and the time spent with specialist staff are associated with a greater understanding of treatment and adherence to prophylaxis.

A NURSE PRACTITIONER PERSPECTIVE

In our experience, the primary outcome to achieve in patients with haemophilia is a reduction in or eradication of bleeds. Rather than focusing on trough levels, patients tend to appreciate fewer bleeds and a reduction in the frequency of infusions. In the Royal Free London NHS Foundation Trust, UK, the treatment plans for most patients with severe haemophilia B include a once-weekly dosing regimen. This has been highly welcomed by the patient group, who had all previously received infusions 2–3 times per week. Adherence is multi factorial and reducing dosing frequency may have some effect on this issue; however, there is no substantial evidence to support this as yet.

Case study 1

At St Luke's Hemophilia Center (Boise, ID, US), the son of a known carrier mother was evaluated for

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haemophilia at birth. The newborn's FIX activity level was 3 IU/dL; he was diagnosed with moderate haemophilia B, referred to a haematology specialist and assigned to a nurse practitioner. The current recommendation for treatment of a child with haemophilia is to not expose the child to factor replacement therapy until medically necessary, but that once treatment is started it should aim to achieve a target trough level of above 1 IU/dL. With a FIX level of 3 IU/dL at birth, the decision was made for episodic rFIX administration if the child experienced a bleeding episode. Later, he was diagnosed with bilateral hearing loss, proteinuria of unknown cause and hyperopia.

The child had few bleeding episodes during his younger years, but at 11 years of age his bleeding episodes began to increase. In particular, he experienced more trauma-related lower extremity musculoskeletal bleeds resulting from increased physical activity. These were treated as needed by his father at home using an rFIX product (BeneFIX®, nonacog alfa, Pfizer). His target joint is now the right ankle and he has developed haemarthrosis. Part of the treatment plan included a referral to an orthotist to assess the stability of his ankle and recommendations for physical therapy to protect his ankles during sport. Despite the need for prophylaxis, the parents had concerns about the best treatment for their child. Both were reluctant to start prophylaxis, with reasons including the mother's lack of confidence at administering intravenous infusions to her child and concerns about the over-use of medication. However, due to the increase in bleeding episodes and continued joint damage, the parents decided to discuss changing the treatment plan to include prophylaxis with their nurse practitioner at the HTC. A decision was not reached during the clinic visit as the father wanted to research the products and companies before choosing a therapy. In addition, PK assessments are required at the HTC when switching therapy treatments and the family had travel plans and could not commit to the lab testing requirements, causing a delay in starting prophylaxis treatment.

Several months later, the family decided to initiate weekly prophylaxis with rIX-FP, understanding that trough levels, and preferably PK assessments, would need to be measured during the switching of products. The family returned to the HTC one week after switching to rIX-FP to measure the trough level. At this point, trough levels were 28% and the nurse practitioner suggested that, with such high levels, infusions should be withheld for 7 days. The family agreed and returned to the clinic 10 days post infusion; the FIX trough level measured 16% during this visit. The nurse practitioner explained to the family that this level was more than sufficient, and the family was asked to return to the clinic to have the trough level assessed after 14 days. The 14-day post-infusion trough level was 4%. Based on this, the nurse practitioner explained to the family that their child could safely infuse rIX-FP every 14 days. Ultimately, the family decided to maintain weekly infusions as they preferred to sustain high factor levels during the time that their son's physical activity was high, with the option to infuse rIX-FP every 14 days when he was not actively participating in sports. The patient has only had one trauma-related bleed in the last two years after starting treatment with rIX-FP. He continues to be active and has not had problems with his ankle.

This case is representative of many of the patients treated at this HTC. Parents/caregivers are hesitant to change from episodic therapy to prophylaxis therapy and many are reluctant to switch products. This family had both hesitancies, even though they were aware of the damage caused by bleeding episodes into the joints. The strategy used with this family was to develop trust and a sense of empowerment that they were going to make the ultimate decision. The mother needed emotional support to help the process that her child was going to receive infusions regularly and the long-term benefits of this decision.

Case study 2

At the Children's National Hospital (Washington, DC, US), a male patient was diagnosed with severe haemophilia B at birth due to a positive family history (maternal uncle with haemophilia). The patient started weekly prophylaxis with an SHL rFIX product (BeneFIX®, nonacog alfa, Pfizer) when he started school. His father learned how to infuse at home.

At 7 years of age the patient's prophylaxis was increased to twice weekly when he experienced breakthrough bleeding. His infusion schedule was also adjusted as he became more physically active and participated in sports, to ensure adequate cover. However, he experienced bleeds to his left and right ankles, and a bleed to his right knee, which led to decreased ankle flexibility and postural deviations. The patient was resistant to learn self-infusion as he got older, and his parents were concerned that his peripheral access might be compromised if he was unsuccessful. The possibility of switching to an EHL product was discussed in clinic, but the family had concerns about whether weekly prophylaxis using EHL factor would provide adequate coverage, and also did

not want to switch product until the patient was ready to consider self-infusion.

Despite their initial concerns around EHL factor, decreasing the frequency of infusions became more appealing as the family transitioned from infusing their son to having him self-administer his treatment by the time he was 12 years of age. They decided to switch to rIX-FP prophylaxis in 2017. To make it easier for their son to remember his infusion day, they elected to dose factor every 7 days. With weekly trough levels of 5–8% on the current regimen, the patient has had no breakthrough bleeding and is successfully self infusing with excellent adherence.

CONCLUSIONS

Patients and caregivers need to be informed about the use of rIX-FP and the discussion on the benefits of prophylaxis when collectively deciding a treatment approach with their healthcare team. rIX-FP is well tolerated and widely used, demonstrating favourable clinical outcomes for adults and paediatrics with haemophilia B in both clinical trials and in routine clinical practice. Patients are treated optimally on a weekly prophylaxis regimen with rIX-FP, and some are able to extend their dosing intervals to every 10, 14 or 21 days while maintaining low bleeding rates, which may lead to improved adherence to prophylaxis infusions.

Real-life experiences have shown that the relationship between a nurse and their patients is complex but crucial to the patient's education and overall quality of life. While determining the optimal treatment approach may be complicated, understanding the benefits of therapeutic products, such as rIX-FP, are essential for healthcare practitioners considering switching their patients' treatment to rIX-FP.

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Conflicts of interest

KG: Speaker/consultant for Takeda, Bayer; advisory boards for Genentech, UniQure and Pfizer.
CG: Advisory boards for Pfizer, CSL Behring, UniQure, Genentech, Octapharma, Novo Nordisk and Takeda.
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Consent

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ORCID

Kara Garner https://orcid.org/0000-0002-4529-3471
Christine Guelcher https://orcid.org/0000-0001-9226-2347
Debra Pollard https://orcid.org/0000-0002-7797-3500

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Table 2. A comparison between dosing intervals, ABR and annual infusions in adult/adolescent and paediatric patients

	rFIX			rIX-FP						
	ADULT/ ADOLESCENTS [59]	ADULT/ ADOLESCENTS [60]	PAEDIATRICS [61]	ADULT/ADOLESCENTS [42]				PAEDIATRICS [43]		
Dosing intervals* (days)	3.5	7	3.5–7	7	10	14	21‡	7	10	14
Number of patients (n)	44	25	22	22	17	41	11	21	8	8
Dose (IU/kg)	50	100§	64.6	35–50	50–75	50–75	100	25–50	50–75	50–75
Annual infusions (n)†	104	52	52–104	52	37	26	17	52	37	26
ABR (median)	2.6	2.0	3.7	1.33	0.80	0.92	0.32	2.00	3.50	5.60
AsBR (median)	1.7	1.0	0.58	0.00	0.28	0.37	0.00	0.00	0.00	1.10
Steady-state trough FIX (%) mean (SD)	3.57 (3.11)	2.0 (N/A)	N/A	22.0 (8.4)	19.8 (16.0)	13.6 (6.4)	7.6 (2.3)	15.1 (4.1)	8.8 (5.7)	7.2 (2.9)

ABR: annualised bleeding rate AsBR: annualised spontaneous bleeding rate

FIX: factor IX N/A: not available SD: standard deviation

* All patients treated with rIX-FP started prophylaxis on a 7-day regimen. rIX-FP extended dosing regimens in adults (10, 14 or 21 days) and paediatrics (10 or 14 days) were for selected eligible patients who were well controlled on their prior regimen for at least 6 months and switched at the investigators' discretion.

† Estimated, assuming 100% compliance with regimen and omitting episodic treatment for bleeds.

§ Based on 50 IU/kg twice weekly; FIX trough levels were not assessed as the prophylactic dosing regimens in this study were not designed to maintain FIX levels at or above 1%.

‡ In adult patients ≥18 years who were well-controlled on the 14-day regimen for at least 6 months prior to switching treatment.