Nonfactor Therapies: New Approaches to Prophylactic Treatment of Haemophilia

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Abstract

For several decades, the treatment of haemophilia has relied on factor replacement therapy, which restores haemostasis by replacing the missing coagulation factor. In recent years, novel alternative therapies for the treatment of haemophilia in patients with and without inhibitors have been developed. These emergent therapies promote haemostasis by mimicking coagulation factors or inhibiting natural anticoagulants. They provide a less invasive route of administration (i.e. subcutaneous) and some offer reduced frequency of dosing (i.e. every 2 weeks, monthly) compared with the majority of factor replacement therapies, and thus have the potential to simplify treatment, increase adherence and subsequently improve outcomes for patients. Their introduction has transformed the care of haemophilia patients with inhibitors to factor VIII, with similar expectation for haemophilia B patients with inhibitors. However, these therapies also come with several new challenges including their limitation to prophylactic treatment, the observed increased incidence of thrombosis, or their impact on the natural history of the disease and potential disruption of existing treatment guidelines like the use of immune tolerance induction. Moreover, questions remain regarding the long-term impact of non-replacement therapies on joint health as well as the optimal strategy to manage breakthrough bleeds in patients with inhibitors.

Keywords

- coagulation
- tissue factor pathway inhibitor
- monoclonal antibody
- RNA interference
- activated protein C inhibitor

Introduction

Haemophilia A and B are X-linked congenital bleeding disorders caused by a deficiency of coagulation factor VIII (FVIII) and IX (FIX), respectively. Haemophilia A is more common than haemophilia B accounting for approximately 80 to 85% of all haemophilia cases.[1] Endogenous FVIII/IX plasma levels determine the clinical bleeding phenotype in haemophilia patients, with factor levels in severe haemophilia of less than 1 IU/dL, in moderate haemophilia of 1 to 5 IU/dL and in mild haemophilia of 5 to 40 IU/dL.[2] Patients with severe haemophilia experience recurrent frequent spontaneous bleeding into joints, muscles or soft tissues and prolonged bleeding after trauma or surgery and replacement therapy has been the standard of care.[1,3]

However, even on prophylaxis some patients still experience occasional bleeds, resulting in progressive and irreversible joint damage (i.e. haemophilic arthropathy);[4,5] as a consequence, factor levels of 1 to 3 IU/dL are now considered insufficient to fully prevent bleeding in all patients with haemophilia and it has been suggested that 'one size fits all' models of trough level might not be appropriate to prevent all bleeding episodes in all patients, particularly those with haemophilia B.[1,6,7] Furthermore, a recent randomised controlled study demonstrated an increase in the number of patients achieving zero total bleeds when the trough level was increased from around 1 to 3% to 8 to 12%.[8]

Factor Replacement Therapy: Advantages and Limitations

The history of factor replacement therapy is well documented. We now have reasonable understanding of predictors of

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bleeding, but there is poor consensus on optimisation of treatment strategies or target outcomes. However, it is not uncommon in routine clinical practice to have a trade-off between enhanced protection and decreased treatment burden. Although personalised prophylaxis had been suggested, it is resource intensive from a patient and clinician perspective and despite recent guidelines, a 'one size fits all' policy is typically in play. Extended half-life products offer enhanced protection and decreased treatment burden by maintaining higher factor levels for longer with fewer intravenous infusions, which may also increase both willingness to consider prophylaxis and adherence.[9]

Nevertheless, factor replacement therapy is ineffective in patients who develop inhibitors, who then require the use of bypassing agents, such as activated prothrombin complex concentrate (aPCC) or recombinant FVIIa (rFVIIa), which are of limited efficacy, or patients must undergo immune-intolerance induction (ITI) to restore responsiveness to factor replacement. Due to these limitations of factor replacement therapies, several novel approaches to the treatment of haemophilia are being investigated and one is now available in the clinic for the treatment of patients with haemophilia A.

What Are Non-Factor Therapies?

Non-factor therapies encompass new therapeutic approaches to the treatment of haemophilia that do not involve replacing the missing coagulation factor. In patients with haemophilia, the missing factor results in impaired generation of thrombin, the key enzyme responsible for the formation of blood clot. Restoration of thrombin generation appears to achieve effective clot formation, and this can be facilitated either through bispecific antibodies that mimic the function of factor VIII or by inhibiting natural anticoagulants (►Fig. 1). Non-factor therapies have the potential to overcome some of the limitations of factor replacement therapies (e.g. by means of subcutaneous administration or reduced dosing frequency). Importantly, they may provide alternative therapeutic options for patients with inhibitors.

Licensed Non-Factor Therapies

Emicizumab (FVIIIa Mimetic)

Emicizumab (Hemlibra, Roche Products Limited) is the only non-factor product licensed to date. Emicizumab is a subcutaneously administered monoclonal antibody indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A with and without inhibitors in the United States,[10] and in patients with haemophilia A with inhibitors or severe haemophilia A without inhibitors in the European Union (►Table 1).[11] Emicizumab is not recommended for episodic treatment of bleeding, in the surgical setting or in patients undergoing ITI.[10,11] Even though emicizumab can be used in all age groups, more research is needed in patients younger than 1 year.[11]

Emicizumab is a humanised bispecific immunoglobulin G4 (IgG4) antibody that binds to human FIX/activated FIX (FIXa) and factor X (FX)/activated FX (FXa) at their epidermal growth factor–like domains with micromolar affinities.[12] Emicizumab bridges FIXa and FX mimicking activated FVIII (FVIIIa),[12] and thus restoring the function of missing FVIIIa, which is required for effective haemostasis (see ►Fig. 1). Because emicizumab has no sequence homology with FVIII, it does not induce the development of inhibitors to FVIII.[12]

In the HAVEN 1 phase 3 study, using a chromogenic assay with human coagulation factors, emicizumab was shown to increase mean FVIII activity from less than 1% at baseline to approximately 30% during maintenance dosing.[13] Emicizumab showed dose-proportional pharmacokinetics (PK) across a dose range of 0.3 to 6 mg/kg and its mean absorption half-life was 1.6 days following subcutaneous administration.[10,11] The absolute bioavailability after subcutaneous administration

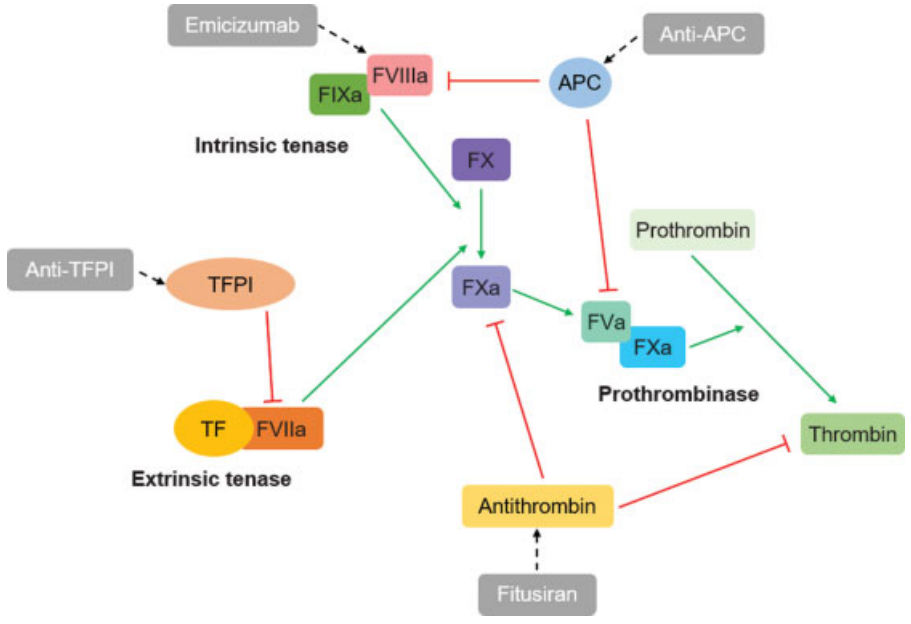

Fig. 1 Mechanisms of action of non-factor therapies. APC, activated protein C; F, factor; TF, tissue factor; TFPI, tissue factor pathway inhibitor.

Table 1 Summary of non-factor therapies

Product	Description	Indication	Route of administration	Dosing regimen	Status
Emicizumab	Bispecific antibody	HA with and without inhibitors	Subcutaneous	Prophylaxis only Once weekly, every 2 or 4 wk	Licensed
Mim8	Bispecific antibody	HA with and without inhibitors	Subcutaneous	Prophylaxis only Once weekly or monthly	Phase 2 ongoing (*NCT04204408*)
Fitusiran	RNAi	HA and HB with and without inhibitors	Subcutaneous	Prophylaxis only Once monthly	Phase 3 on hold (*NCT03549871*, *NCT03754790*, *NCT03417102*, *NCT03417245*)
Concizumab	Monoclonal antibody	HA and HB with and without inhibitors	Subcutaneous	Prophylaxis only Once daily	Phase 3 ongoing (*NCT04083781*, *NCT04082429*)
BAY-1093884	Monoclonal antibody	HA and HB with and without inhibitors	Subcutaneous	Prophylaxis only Once weekly	Phase 2 terminated (*NCT03597022*)
PF-06741086	Monoclonal antibody	HA and HB with and without inhibitors	Subcutaneous	Prophylaxis only Once weekly	Phase 3 ongoing (*NCT03938792*)
KRK α_1AT	APC-specific serpin	HA and HB with and without inhibitors	Potential for subcutaneous	Not yet established	Preclinical

Abbreviations: α1AT, α-1 antitrypsin; APC, activated protein C; FVIIIa, activated factor VIII; HA, haemophilia A; HB, haemophilia B; RNAi, RNA interference.

of 1 mg/kg was 80.4 to 93.1%.[10,11] The mean elimination apparent half-life was nearly 27 days after multiple subcutaneous administrations.[10,11] In phase 3 clinical trials, mean trough concentrations of emicizumab of more than 45 µg/mL were consistently observed in patients with haemophilia A with and without inhibitors receiving emicizumab every week, every 2 weeks or every 4 weeks; however, mean trough concentrations were lower with administration every 4 weeks than every 2 weeks.[14–18]

In several phase 3 clinical trials, prophylaxis with emicizumab has been shown to reduce bleeding in adults, adolescents and children with haemophilia A with and without inhibitors (►Table 2).[14–18] In all clinical studies, emicizumab was well tolerated;[14–18] however, HAVEN 1 reported events of thrombotic microangiopathy and thrombosis, which were considered associated with the concomitant use of emicizumab for prophylaxis and aPCC for the treatment of breakthrough bleeding (averaging >100 U/kg daily for ≥24 hours).[14] The latter triggered a box warning on the risk of thrombotic microangiopathy and thromboembolism in patients receiving emicizumab in conjunction with aPCC.[10] No such adverse events were observed when emicizumab was used concomitantly with rFVIIa.[19] Further evaluation of emicizumab safety combining data from post-market reports, expanded access programs, compassionate use and clinical studies showed that of four thrombotic microangiopathy events reported in patients with haemophilia A receiving emicizumab, all occurred when aPCC was used concomitantly. In addition, of eight thromboembolic events reported, two occurred in patients receiving aPCC concomitantly with emicizumab, while the remaining six thrombotic events were unrelated to aPCC use and occurred in patients with pre-existing cardiovascular disease or blood clotting risk factors.[20] Of note in one recent real-word evidence study in 148 patients treated with emicizumab, no thrombotic microangiopathy was reported and there was only one thrombotic event, which occurred in the one patient receiving emicizumab and aPCC.[21] In a second study in 122 patients treated with emicizumab, there were no reports of thrombosis or thrombotic microangiopathy.[22] Essentially emicizumab has no on/off regulation and in vitro spiking studies with sequence-identical analogue (SIA) of emicizumab with aPCC demonstrated a 17-fold increase in thrombin generation compared with SIA alone and about 4-fold greater than reference plasma, unlike a combination of SIA and rFVIIa, all of which suggest a synergistic effect.[23,24]

With the exception of one patient in the HAVEN 2 study, no antidrug antibodies (ADAs) with neutralising potential were detected in the clinical trials; no patients developed inhibitors to FVIII.[14–18]

In patients receiving emicizumab prophylaxis, breakthrough bleeding and surgical interventions should be managed with bypassing agents in patients with inhibitors or with FVIII in patients without inhibitors, with the latter presenting a risk of inhibitor development. In patients with inhibitors, rFVIIa is being recommended as first-line treatment, particularly for home treatment. Where patients require aPCC, this is preferentially under medical supervision with monitoring.[25] However, it should be noted that due to emicizumab's mode of action, standard aPTT-based and one-stage FVIII assays are inadequate for assessing FVIII activity in patients treated with emicizumab.[26,27]

Non-Factor Therapies in Development

Several other non-factor therapies are in clinical trials for bleeding prevention in patients with haemophilia A and B with and without inhibitors (►Table 1). Similar to

Table 2 Phase 3 clinical studies of subcutaneous emicizumab for the prophylaxis of bleeding events in adults, adolescents, and children with haemophilia A with and without inhibitors

Study/Dosing regimen	No. of patients	ABR[a] (95% CI)	Zero bleeding events, % patients (95% CI)
Adolescents and adults (≥12 y)			
With inhibitors (HAVEN 1)[14]			
Previously received episodic treatment with bypassing agent			
1.5 mg/kg weekly[b]	35	2.9 (1.7–5.0)	62.9 (44.9–78.5)
No prophylaxis	18	23.3 (12.3–43.9)	5.6 (0.1–27.3)
Previously received prophylactic treatment with bypassing agent			
1.5 mg/kg weekly[b]	49	5.1 (2.3–11.2)	69.4 (54.6–81.7)
Without inhibitors (HAVEN 3)[15]			
Previously received episodic treatment with FVIII			
1.5 mg/kg weekly[b]	36	1.5 (0.9–2.5)	56 (38–72)
3 mg/kg every 2 wk[b]	35	1.3 (0.8–2.3)	60 (42–76)
No prophylaxis	18	38.2 (22.9–63.8)	0 (0–18)
Previously received prophylactic treatment with FVIII			
1.5 mg/kg weekly[b]	63	1.6 (1.1–2.4)	55.6 (42.5–68.1)
HAVEN 4[16]			
6.0 mg/kg every 4 weeks[†]	41	2.4 (1.4–4.3)	56.1 (39.7–71.5)
Paediatrics (<12 y)			
Without inhibitors (HAVEN 2)[17]			
Previously received episodic or prophylactic treatment with bypassing agent			
1.5 mg/kg weekly[b]	65	0.3 (0.2–0.5)	76.9 (64.8–86.5)
3 mg/kg every 2 wk[b]	10	0.2 (0.0–1.7)	90.0 (55.5–99.7)
6.0 mg/kg every 4 wk[b]	10	2.2 (0.7–6.8)	60.0 (26.2–87.8)
Without inhibitors (HOHOEMI)[18]			
3 mg/kg every 2 wk[b]	6	1.3 (0.6–2.9)	33.3
6.0 mg/kg every 4 wk[b]	7	0.7 (0.2–2.6)	71.4

Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FVIII, factor VIII.
[a]Based on a negative binomial regression model.
[b]Maintenance dose administered following a loading dose of 3.0 mg/kg/wk for 4 wk.

emicizumab, these therapies may offer subcutaneous administration and/or lower frequency of dosing, but they are not expected to be effective for episodic bleeding.

FVIIIa Mimetic

Mim8 (Novo Nordisk A/S) is another human bispecific antibody that mimics FVIIIa by bridging FIXa and FX, and is being developed for subcutaneous prophylactic treatment of haemophilia A with and without inhibitors.[28–31]

A phase 2 clinical trial (*NCT04204408*) evaluating the safety, tolerability, PK and pharmacodynamics (PD) of Mim8 in healthy participants (part 1) and in patients with haemophilia A with and without inhibitors (part 2) is currently ongoing.

Antithrombin Inhibition

Fitusiran (Sanofi Genzyme) is an RNA interference (RNAi) therapy that targets antithrombin messenger RNA to block the synthesis of antithrombin in the liver, resulting in increased thrombin generation (►**Fig. 1**). Fitusiran is being developed as a monthly subcutaneously administered therapy for the treatment of haemophilia A and B with and without inhibitors. Episodic bleeding should be treated with factor replacement.

In a phase 1 dose-escalation study, fitusiran was shown to reduce antithrombin levels and increase thrombin generation in a dose-dependent manner, as well as reduce bleeding (►**Table 3**).[32] Although well tolerated, transient elevation of liver function tests and D-dimers have been reported in some patients, particularly in patients with previous hepatitis C infections.[32]

Interim results of the phase 2 open-label extension study in haemophilia A and B patients with or without inhibitors receiving once monthly subcutaneous fitusiran prophylaxis reported sustained reductions of antithrombin levels and improved thrombin generation, and a median annualised bleeding rate (ABR) of 1.5.[33] No ADAs were detected.[33] However, in one patient with severe haemophilia A, the use of fitusiran in conjunction with daily high-dose FVIII

Table 3 Summary of a phase 1 dose-escalation study of subcutaneous fitusiran[32]

Group/Dosing regimen	No. of participants	Mean maximum antithrombin lowering, % (SE)	Exploratory bleeding rates analysis	
			Median ABR[a]	Zero bleeds, *N* (%)
Healthy volunteers				
0.03 mg/kg[b]	3	19 (4.4)	–	–
Haemophilia A or B patients without inhibitors				
0.015/0.045/0.075 mg/kg weekly[c]	12 (3/6/3)	61 (8)[d]	–	–
0.225/0.45/0.9/1.8 mg/kg monthly[c]	18 (3/3/3/3)	70 (9)[e] 89 (1)[d]	0	10 (56)
Fixed dose 80 mg monthly[c]	6	87 (1)	–	–

Abbreviations: ABR, annualised bleeding rate; SE, standard error.
[a]Median ABR of 3 during pre-study period.
[b]Healthy volunteers received a single subcutaneous infusion.
[c]Patients with haemophilia received three subcutaneous infusions either once weekly or once monthly at the stated doses.
[d]At a dose of 0.075 mg/kg weekly.
[e]At a dose of 0.225 and 1.8 mg/kg monthly, respectively.

was associated with fatal thrombosis.[34] After a clinical hold, bleed management guidelines for episodic treatment of bleeding during fitusiran prophylaxis were developed and patients are now receiving low-dose factor or bypassing agents in phase 3 clinical trials.[35]

Several phase 3 clinical studies evaluating the efficacy and safety of fitusiran in patients with haemophilia A and B without inhibitors (*NCT03417245*), with inhibitors (*NCT03417102*) and previously treated with a factor replacement or bypassing agent (*NCT03549871*), as well as an open-label study (*NCT03754790*) are ongoing. In November 2020, the full clinical development program for fitusiran was put on hold following the identification of new adverse events.[36]

Anti-Tissue Factor Pathway Inhibitor

After tissue damage, tissue factor (TF) activates coagulation through the initiation pathway; endogenous tissue factor pathway inhibitor (TFPI) is the main inhibitor of this process through inhibition of the FVIIa/TF complex that initiates coagulation (►Fig. 1).[37,38] Therefore, inhibiting TFPI has been proposed to be an alternative method to treat haemophilia. Different anti-TFPI monoclonal antibodies, which promote thrombin generation by binding to the K1 and/or K2 domains of TFPI and thus preventing FVIIa and FXa inhibition, are in development for the treatment of haemophilia A and B in patients with and without inhibitors (►Table 4).

Concizumab (Novo Nordisk A/S) is a humanised monoclonal IgG4 antibody specific for the K2 domain of TFPI.[38] In phase 1 single-dose and multiple-dose escalation studies in haemophilia A and B patients, concizumab demonstrated a dose-dependent decrease in TFPI levels and was well tolerated with no ADAs detected.[39,40] Concizumab showed a nonlinear PK due to target-mediated clearance.[39] Two phase 2 studies evaluated the safety and efficacy of daily subcutaneous concizumab prophylaxis in patients with haemophilia A and B (►Table 5).[41] In both phase 2 trials, concizumab was well

Table 4 Status of clinical development of anti-TFPI monoclonal antibodies

Product	Completed clinical studies	Ongoing clinical studies
Concizumab	• Explorer 1: Phase 1 single dose-escalation study in haemophilia A and B patients[39] • Explorer 3: Phase 1 multiple dose-escalation study in haemophilia A patients[40] • Explorer 4: Phase 2 proof-of-concept multiple-dose study in patients with haemophilia A and B with inhibitors[41] • Explorer 5: Phase 2 proof-of-concept study in patients with haemophilia A without inhibitors[41]	• Explorer 7: Phase 3 study in patients with haemophilia A and B with inhibitors (NCT04083781) • Explorer 8: Phase 3 study in patients with haemophilia A and B without inhibitors (NCT04082429)
BAY-1093884	• Phase 2 multiple dose-escalation study in patients with haemophilia A and B with and without inhibitors (terminated)[44]	
PF-06741086	• Phase 1 single dose-escalation study in healthy volunteers[45] • Phase 2 multiple dose-escalation study in patients with haemophilia A and B with or without inhibitors (NCT02974855)	• Phase 3 study in patients with severe haemophilia A and B with and without inhibitors (NCT03938792)

Abbreviation: TFPI, tissue factor pathway inhibitor.

Table 5 Phase 2 clinical studies of subcutaneous concizumab

	No. of patients	Dosing regimen	Estimated ABR (95% CI)
Patients with severe haemophilia A without inhibitors	36	0.15 mg/kg daily[a]	7.0 (4.6–10.7)
Patients with haemophilia A and B with inhibitors	17	0.15 mg/kg daily[a,b]	4.5 (3.2–6.4)
		Episodic treatment with rFVIIa	20.4 (14.4–29.1)

Abbreviations: ABR, annualised bleeding rate; rFVIIa, recombinant activated factor VII.
[a]Potential dose escalation to 0.20 and 0.25 mg/kg.
[b]Loading dose of 0.5 mg/kg.

tolerated with a reduction in ABR and no thromboembolic events reported. A total of six patients developed ADAs, and three of these had antibodies that were neutralising in vitro; however, the development of ADAs was not associated with clinical changes.[41] Concizumab does not have the benefit of less frequent dosing compared with factor replacement therapies, but it provides an alternative route of administration (i.e. subcutaneous). Phase 3 trials are ongoing and will provide greater clarity on the potential benefits of this therapy (►Table 4). The phase 3 trials were halted in March 2020 due to the occurrence of non-fatal thrombotic events in three patients; the trials were given clearance to resume recruitment in August 2020.[42]

BAY-1093884 (Bayer AG) is a human monoclonal IgG2 antibody with a high affinity for the K1 and K2 domains of TFPI. BAY-1093884 showed dose-dependent reduction in TFPI levels and a nonlinear PK.[43] A phase 2 clinical trial was terminated in November 2019 due to three thrombotic events related to BAY-1093884, which occurred in the absence of concomitant use of bypassing agents or factor replacement (►Table 4).[44]

PF-06741086 (Marstacimab, Pfizer) is a human monoclonal IgG1 antibody with high affinity for the K2 domain of TFPI.[45] PF-06741086 was shown to undergo target-mediated drug disposition.[45] A phase 2 multiple dose-escalation study was completed in 2019 and a phase 3 study is currently ongoing (►Table 4).

All the anti-TFPI monoclonal antibodies, to a variable extent, are affected by target-mediated drug disposition (i.e. clearance secondary to binding to target). This has necessitated frequent dosing compared with other monoclonal antibodies, but also contributes to inter-individual variability in PK and treatment response.

Anti-Activated Protein C

Additional agents are in development to target APC to rebalance haemostasis; APC is a powerful anticoagulant that restricts thrombin production and is a novel target to treat haemophilia (►Fig. 1).[46–48] APC is activated from its precursor, protein C, by thrombin bound to thrombomodulin on the endothelial cell surface.[46] Once formed, APC exerts its anticoagulant activity by proteolytically inactivating FVIIIa and activated factor V (FVa).[46,47]

A Pittsburgh variant of α-1 antitrypsin (α_1AT), KRK α_1AT (ApcinteX), is currently in development and its effects on anticoagulant pathways, by inhibiting APC and preventing degradation of FVIIIa and FVa, have been assessed in preclinical studies.[46,47] KRK α_1AT is expected to have a long half-life, low immunogenic potential and potential subcutaneous administration.[47] However, the effect of long-term administration of an APC inhibitor on inflammation is difficult to predict and it is also unclear how effective an APC inhibitor would be in treating haemophilia.

Benefits of Non-Factor Therapies

Improved Protection

Prophylaxis effectively prevents bleeding episodes, reduces joint damage and improves quality of life in patients with haemophilia.[1,49] There are several challenges with factor replacement prophylaxis, which extended half-life factors address, such as a reduction in treatment burden and improved protection.[9] Furthermore, the burden of disease is even higher in patients with haemophilia who develop inhibitors, with higher rates of bleeding and mortality than patients without inhibitors.[50,51]

Based on the mode of action of different products currently in clinical use or trials, the aim of non-factor therapies is to restore thrombin generation to levels observed in patients with mild haemophilia; importantly this is a continuous effect with no peaks and troughs. This enables improved protection for spontaneous bleeds as well as minor traumatic bleeds, which in turn may result in reduced pain and physical restrictions, increased participation in social events and physical activities, thus improving a patient's quality of life and overall health. Moreover, non-factor therapies provide a more effective treatment for haemophilia patients with inhibitors than traditional bypassing agents.

Non-factor therapies provide an easy and convenient route of administration (i.e. subcutaneous) and some offer a reduced frequency of dosing (i.e. monthly infusions and longer-half life than factor replacement therapies). These therapies might also allow an earlier start of prophylaxis than current therapies, as they do not require central venous access devices; however, further studies on the safety of non-factor therapies in very young children are required.[52]

Decreased Treatment Burden

The reduction of treatment burden with non-factor therapies is two-fold. First, the time required for regular administration of

the medication for prophylaxis is decreased, which has the potential to improve adherence and increase the number of patients on prophylaxis, including patients with moderately severe haemophilia. The second aspect is related to the time spent on planning activities around prophylaxis, as with improved control patients need to undertake less risk assessment about their bleeding in relation to daily activities. Accordingly, in clinical trials, emicizumab prophylaxis was associated with improvements in health-related quality of life and health status, with reduced numbers of missed school or work days, and the majority of patients preferred emicizumab over their previous treatment with FVIII replacement or a bypassing agent.[14–16]

Challenges of Non-Factor Therapies

Management of Bleeds

Non-factor therapies are currently limited to prophylaxis, and so patients require additional haemostatic treatment with bypassing agents or factor replacement to treat breakthrough bleeding or during surgical procedures. There is no suggestion of synergistic effects between emicizumab and FVIII. However, concomitant use of emicizumab and aPCC resulted in thrombotic complications, but concomitant use with rFVIIa was found to be effective with no reported adverse events.[19] Standard doses have been used at slightly longer intervals, and most patients seem to require between one and two doses. Similarly, fitusiran in combination with high-dose FVIII replacement resulted in a fatal thrombosis.[14,34] Further studies are needed to determine the interactions between non-factor prophylaxis and episodic/surgical treatment with bypassing agents or factor replacement.

Risk of Thrombosis

An important aspect of the rebalanced haemostasis is a less controlled regulation of coagulation. This is particularly pertinent when patients require additional factor or bypassing agents, and the combination in some instances appears to be more than additive. This decrease in the regulation of coagulation may result in thrombotic events, particularly arterial, in the presence of underlying cardiovascular risk factors; thus, an assessment of this prior to therapy initiation is important. It is also important to appreciate that although the increase in thrombin generation is said to be similar to that of mild haemophilia, the lack of usual tight regulation may result in a thrombotic event rate higher than what is expected in patients with mild haemophilia.

Indeed, thrombotic events have been reported with all the non-factor therapies, some of which can be explained by either a drug–drug interaction or the presence of underlying cardiovascular risk factors. The incidence needs to be closely monitored, as it is unclear if its increase reflects the background population risk or if there are other factors involved beyond the population risk.

Change in the Natural History of the Disease

In clinical trials of emicizumab, the concept of treated and untreated bleeds was introduced for the first time. In routine clinical practice, it is not uncommon for patients to move their prophylaxis by a few hours, if they have early symptoms of a bleed. The long-term outcomes of such minor bleeds, which presumably resolve, are unknown and thus our surveillance strategies for joint health require further scrutiny. Several clinicians have reported anecdotally that patients are now presenting with larger muscle bleeds, a few days after the initiation of an event similar to mild haemophilia patients, often requiring extended duration of treatment. This is probably secondary to a slow rate of accumulation of blood and subsequent changes in tissue pressure and pain that initiate a clinical review.

Another question that needs further studies is how non-factor therapies will impact ITI. Recently, it has been suggested that eradication of inhibitors is still desirable, and thus patients with inhibitors should be offered at least one attempt at ITI.[53] This recommendation was based on the observation that episodic treatment with FVIII in patients without inhibitors on emicizumab prophylaxis was more effective than treating breakthrough bleeds with bypassing agents in patients with inhibitors.[15,53]

In addition, the impact of these therapies on patient adherence and cost of prophylaxis needs to be studied.

Management of Prophylaxis and Definition of Therapeutic Failure

The World Federation of Hemophilia (WFH) guidelines strongly recommend that all patients with haemophilia A or B with a severe phenotype should be on prophylaxis and this should be personalised based on the patient's clinical phenotype, joint status, individual PK, physical activity level, lifestyle and preference.[1]

Prophylaxis with factor replacement therapy aims for the lowest possible consumption that ensures good outcomes, and importantly there is scope to increase consumption to achieve higher factor levels with improved protection and zero ABR. Such escalation of drug doses is not feasible with non-factor therapies, which are essentially administered as fixed weight-based dosing. Although dose escalation was permitted in the HAVEN 1 study, this provision is not included in the license. The mean trough levels reported in the clinical trials do not provide an understanding of the interindividual variability, which becomes pertinent when administered every 4 weeks, as lower trough levels are expected compared with weekly dosing, and thus there is scope for providing suboptimal protection. Indeed, the 4-weekly injection appears to have higher bleed rates, although this was not a randomised study;[16] therefore, changing the frequency of infusion must be considered in the event of bleeds with less frequent administration.

The protection with non-factor therapies is fixed for a particular patient and, as such, it becomes important for us to develop definitions for treatment failures. If a patient continues to develop joint bleeds regularly after therapy has been established, consideration needs to be given to switching therapies. This will be a challenging conversation, as patients might perceive the trade-off between decreased treatment burden and suboptimal protection to be acceptable.

Personalised Treatment

Choice of Patients

The introduction of emicizumab has transformed the care of haemophilia A patients with inhibitors, and similarly the other non-factor therapies provide choice and likely benefit for haemophilia B patients with inhibitors given their low response to ITI and high risk of haemorrhagic complications and allergic reactions.[54] Patients with poor venous access as well as very young children may greatly benefit from subcutaneous administration. However, as mentioned earlier, the long-term efficacy and safety of non-factor therapies in very young paediatric patients requires further research, and long-term data in older populations would have to be collected before newborns can receive these novel therapies.[11] Furthermore, even though theoretically subcutaneous administration should be preferred over intravenous, many patients are used to managing their haemophilia with intravenous infusions and may be reluctant to change; therefore, the patient's preference is likely to be an important factor in determining treatment regimen/type. Given observed risks of thrombotic events with non-factor therapies, patients with a history of thrombosis may be at an increased risk of morbidity with non-factor therapies, and thus these patients might not be suitable candidates to receiving non-factor products.

Risk Factors: Known and Unknown

Several open questions of non-replacement factor therapies have been mentioned already, including how to manage patients undergoing surgery, during periods of high activity or breakthrough bleeding episodes; accurately monitor treatment; the long-term impact on joint health; the risk of thrombosis; concomitant therapy with bypassing agents; and immunogenicity. Furthermore, in paediatric patients or previously untreated patients, the risk of developing inhibitors remains due to the need for factor replacement products to treat breakthrough bleeding or during surgical and other invasive procedures.

With numerous emergent non-factor therapies with different mechanisms of action, additional questions remain with respect to how to assess PK and PD effects, clinical outcomes and adverse events; how to manage patients perioperatively or during breakthrough bleeding; and how to monitor therapy, dosing protocols, neutralising ADAs, factor and antibody activity and inhibitor eradication.

Limited direct comparisons between non-factor and factor replacement therapies make it difficult to compare efficacy between these therapies. In addition, real-world studies could provide valuable insight as to how these novel therapies will work in clinical practice when a larger population are available for treatment, without the strict eligibility criteria from clinical trials.

Conclusions

Emergent non-factor therapies can potentially provide a convenient route of administration and flexible dosing regimens. Clinical studies have so far demonstrated these therapies to be effective and generally well tolerated, and thus a potential alternative to conventional factor replacement therapies for the prophylaxis of bleeding episodes in patients with haemophilia A and B with and without inhibitors. Their introduction has transformed the care of patients with inhibitors; however, questions remain regarding the long-term impact of non-factor therapies on joint health and the risk of thrombosis, and on the optimal way to manage breakthrough bleeds, particularly in patients with inhibitors.

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Conflict of Interest

P.C. reports grants from Royal Free Charity TF 35, during the conduct of the study; grants and other from Pfizer, Bayer, CSL Behring, Freeline, Novo Nordisk, SOBI; personal fees from BioMarin and UniQure; other from Chugai, Roche, Takeda, Sanofi, Spark Therapeutics, outside the submitted work.

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