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REVIEW ARTICLE

Practical considerations for nonfactor-replacement therapies in the treatment of haemophilia with inhibitors

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Abstract

New therapeutic agents for haemophilia with inhibitors that are in development or already licensed are expected to provide transformative treatment options. Many of these new therapies are not based on simply replacing the missing factor; new strategies include bispecific antibody technology that mimics factor VIII coagulation function (emicizumab), and inhibition of anticoagulant proteins such as tissue factor pathway inhibitor (eg PF-06741086) and antithrombin (eg fitusiran). These agents are administered subcutaneously and should significantly reduce treatment burden and increase the ability to deliver prophylaxis for patients. Limited real-world data and validated practical guidance on these recently licensed/upcoming treatments resulted in the authors convening to discuss recommendations on their use. Emicizumab is currently the only licenced nonfactor therapy; thus, our recommendations focus on this product. Target candidates for emicizumab prophylaxis are difficult-to-treat patients with haemophilia A and inhibitors and/or venous access issues, frequent bleeds and target joints. In case of breakthrough bleeding while receiving emicizumab, patients still require treatment with bypassing agents; the adjunct treatment of choice is recombinant activated factor VII. This treatment is also recommended to prevent bleeds in patients with inhibitors undergoing surgery. Our recommendations on suitable laboratory assays and monitoring new products, as well as the benefit of patient-reported outcomes (such as pain and physical activity levels), are included. We also briefly discuss future treatment options for patients with haemophilia B and inhibitors. Although these nonfactor treatments offer great promise, further data and real-world evidence are needed.

KEYWORDS
emicizumab, haemophilia A, inhibitors, nonfactor-replacement therapies, prophylaxis

1 | INTRODUCTION

Developments in haemophilia care have paved the way towards transformative treatments that address the limitations of current factor-replacement regimens.[1,2] These novel treatments have varied mechanisms of action; some involve replacing the missing factor, while others employ nonfactor-replacement strategies. Factor-replacement approaches involve extending the half-life of exogenous factor protein, use of factor VIII (FVIII) orthologs and replacing the gene that produces the endogenous factor protein.[3,4] Therapies not based on replacing the missing factor (nonfactor-replacement approaches) include bispecific antibody technology that mimics the FVIII coagulation function, and inhibition of anticoagulant proteins (tissue factor pathway inhibitor [TFPI] and antithrombin [AT]) using antibodies, aptamers or RNA interference (RNAi) technology.[1]

The humanized bispecific antibody, emicizumab (Hemlibra®, Roche, Basel, Switzerland), is approved by the European Medicines Agency and the US Food and Drug Administration for prophylaxis in patients with and without haemophilia A FVIII inhibitors (HAwI).[5,6] Nonfactor-replacement therapies in development include the TFPI-targeting monoclonal antibodies, concizumab (Novo Nordisk, Bagsværd, Denmark; trials temporarily paused due to nonfatal thrombotic events),[7-9] BAY1093884 (Bayer AG, Berlin, Germany; trial terminated due to thrombosis [ClinicalTrials.gov Identifier: NCT03597022])[10] and PF-06741086 (Pfizer, New York, NY, USA),[11] as well as fitusiran, an RNAi therapy targeting AT (Alnylam Pharmaceuticals, Inc, [Cambridge, MA, USA] and Sanofi Genzyme [Cambridge, MA, USA]).[12,13] Table 1 provides an overview of these nonfactor-replacement therapies.[9-12,14-23]

The licensed nonfactor-replacement therapy, emicizumab (and potentially those in clinical trials), offers the prospect of improved compliance via more convenient subcutaneous (s.c.; vs intravenous [iv]) administration, as well as reduced administration frequency vs conventional factor replacement, with the flexibility to individually adjust to weekly dosing.[2,22] Importantly, the nonfactor-replacement therapies offer a promising treatment option for patients with haemophilia with inhibitors (HwI).[19] Inhibitor development remains the greatest complication in haemophilia[24]: while bypassing agents (recombinant activated factor VII [rFVIIa; NovoSeven®, Novo Nordisk, Bagsværd, Denmark; not licenced for prophylaxis in all countries] and plasma-derived activated prothrombin complex concentrate [pd-aPCC; FEIBA®, Takeda Pharmaceutical Company Limited, Osaka, Japan]) can prevent and control bleeding in patients with HwI, they are not as effective as factor-replacement therapy in noninhibitor patients. In contrast, emicizumab prophylaxis has shown greater efficacy than previous prophylaxis with bypassing agents in HAwI.[21] Therefore, nonfactor-replacement therapies may represent an alternative treatment option for HwI.

There is currently relatively little published evidence for nonfactor-replacement agents, resulting in limited guidance on their use and a few articles outlining practical considerations.[25-30] Accordingly, the Zürich Haemophilia Forum convened in April 2018 with the purpose of reaching consensus on practical aspects of using these novel therapies for treating HwI. As emicizumab is the only nonfactor therapy currently approved for use in patients with haemophilia A (PwHA) and inhibitors, this article summarizes the panel's consensus opinion on treatment with emicizumab, with reference to other, emerging nonfactor therapies where applicable. Evidence relating to these emerging nonfactor treatments is currently very scarce, but our considerations may also pertain to these therapies in the future. As emicizumab cannot be used in PwHB, we also briefly discuss future treatment options for PwHB and inhibitors.

2 | CONSIDERATIONS FOR NOVEL THERAPIES FOR HAwI

2.1 | Which patients would benefit from a new nonfactor product?

2.1.1 | Consensus

- The target candidates for treatment with nonfactor-replacement product prophylaxis are difficult-to-treat HAwI: patients who have undergone unsuccessful immune tolerance induction (ITI), those who (for various reasons) are foregoing or waiting for ITI to start and those who may be affected by venous access issues, frequent bleeds and target joints.
- The risk/benefit of beginning emicizumab prophylaxis immediately before major elective surgery should be carefully evaluated, as it is preferable for patients to be fully stable on their treatment, with safety and efficacy fully established[17] (see Section 2.3).

2.1.2 | Rationale/evidence

Four common clinical scenarios were considered in the panel's discussions. Firstly, patients with unsuccessful ITI (no new planned ITI). Such PwHA would be strong candidates for emicizumab (or another appropriately licenced nonfactor-replacement product). In these cases, eligibility for switching may be affected by several considerations, including age, comorbidity, lifestyle (active vs sedentary), annualized bleeding rate (ABR) and joint status.

The second scenario involved either children with haemophilia A and newly developed, high-titre inhibitors, or adult patients with high-titre inhibitors who have not undergone ITI due, for example to venous access problems or a reluctance to undergo ITI. The panel agreed that new nonfactor products, such as emicizumab, should not replace ITI as the first-line option for these patients; FVIII tolerance remains the primary goal, and ITI has a high chance of success with international registries reporting success rates of 51%-79%.[31-34] Our rationale is that, while emicizumab has demonstrated considerable bleed reductions in HAwI, additional haemostatic treatment may be required for breakthrough bleeds or during surgery. Therefore, if possible, patients should acquire tolerance to replacement factor.

TABLE 1 Overview of nonfactor-replacement therapies recently licensed or in development

Product/company	Mechanism of action	Current status	Select clinical trials involving patients with HwI
Emicizumab (Hemlibra®, Roche, Basel, Switzerland)	Humanized bispecific antibody Mimics FVIII by simultaneously binding FIXa and FX[a,15,17,20]	Approved by the EMA and US FDA for routine prophylaxis in patients with haemophilia A with or without FVIII inhibitors	**Phase III (HAVEN 1), PwHA and inhibitors, n = 109**[b,21] Prophylaxis s.c. once weekly or no prophylaxis *Key efficacy results:* Significant ABR difference of 87% ($P < .001$) in favour of prophylaxis (ABR: 2.9) vs no prophylaxis (ABR: 23.3) *Key safety results:* TMA and thrombosis in three and two patients, respectively, treated with emicizumab and concurrent multiple infusions of pd-aPCC (>100 U/kg/d for more than 1 d) **Phase III (HAVEN 4), PwHA with and without inhibitors; PK run-in cohort (n = 7) and expansion cohort (n = 41)**[22] Prophylaxis dosed s.c. every 4 wk *Key efficacy results:* 23/41 patients (56%) in the expansion cohort reported no treatment-requiring bleeds. Model-based ABR for treated bleeds was 2.4 (median ABR: 0) and ABR for all bleeds was 4.5. ABRs for treated spontaneous, joint and target joint bleeds were 0.6, 1.7 and 1.0, respectively *Key safety results:* There were no de-novo antidrug antibodies, FVIII inhibitors or thrombotic events detected; one grade 3 SAE (not considered study drug related) **Phase IV (NCT03361137), PwHA and inhibitors undergoing minor surgery** *Key endpoints:* Surgical site bleeding and use of bypassing agents, AEs, surgical complications requiring hospitalization or return to surgery
Fitusiran (Alnylam Pharmaceuticals, Inc and Sanofi Genzyme, Cambridge, MA, USA)	RNAi against AT[12,14,18,19]	Phase II and III	**Phase II (ATLAS-OLE study; NCT03754790), PwHA or PwHB with or without inhibitors** Prophylaxis (fixed dose) s.c. once monthly *Key endpoints:* AEs, ABR, spontaneous ABR, joint ABR, change in QoL **Phase III (ATLAS-INH; NCT03417102), PwHA or PwHB with inhibitors** Prophylaxis dosed s.c. or on-demand bypassing agents *Key endpoints:* ABR, spontaneous ABR, joint bleed ABR (all over 9 mo), QoL **Phase III (ATLAS-PPX; NCT03549871), PwHA or PwHB previously receiving bypassing agent prophylaxis (with or without inhibitors)** Prophylaxis dosed s.c. once monthly *Key endpoints:* ABR, spontaneous ABR, joint bleed ABR (over 13 mo), QoL
Concizumab (Novo Nordisk, Bagsværd, Denmark)	Humanized monoclonal antibody against TFPI[9]	Phase II and III	**Phase II and III (explorer™5; NCT03196297, explorer™7; NCT04083781 and explorer™8; NCT04082429), PwHA or PwHB with inhibitors** Prophylaxis dosed s.c. once daily *Trials temporarily suspended due to nonfatal thrombotic events (clinicaltrials.gov)* *Key endpoints:* Number of bleeding episodes and spontaneous bleeds (up to 24 wk); AEs and anticoncizumab antibodies; PK and safety assessment
BAY1093884 (Bayer AG, Leverkusen, Germany)	Humanized monoclonal antibody against TFPI[10]	Phase II	**Phase II (NCT03597022), PwHA or PwHB with or without inhibitors** Prophylaxis dosed s.c. once weekly; multiple escalating doses *Trial terminated due to thrombosis (clinicaltrials.gov)* *Key endpoints:* AEs, SAEs, AESIs, laboratory values
Marstacimab (PF-06741086) (Pfizer, New York, USA)	Monoclonal antibody against TFPI[11,16]	Phase III	**Phase III (NCT03938792), PwHA or PwHB with or without inhibitors** Prophylaxis dosed s.c. once weekly *Key endpoints:* ABR, thrombotic events, antidrug antibodies, neutralizing antibodies, AEs, SAEs

Abbreviations: ABR, annualized bleeding rate; AE, adverse event; AESI, adverse events of special interest; AT, antithrombin; ATLAS-INH, A Study of Fitusiran (ALN-AT3SC) in Severe Hemophilia A and B Patients With Inhibitors; ATLAS-OLE, Long-term Safety and Efficacy Study of Fitusiran in Patients With Hemophilia A or B, With or Without Inhibitory Antibodies to Factor VIII or IX; ATLAS-PPX, A Study of Fitusiran Prophylaxis in Hemophilia A and B Patients With Inhibitors; EMA, European Medicines Agency; FDA, Food and Drug Administration; FIXa, activated factor IX; FVIII, factor VIII; FX, factor X; HAVEN, A Clinical Trial to Evaluate Prophylactic Emicizumab vs no Prophylaxis in Hemophilia A Participants Without Inhibitors; HwI, haemophilia with inhibitors; iv, intravenous; NCT, National Clinical Trial; pd-aPCC, plasma-derived activated prothrombin complex concentrate; PK, pharmacokinetics; PwHA, patients with haemophilia A; PwHB, patients with haemophilia B; QoL, quality of life; rFVIIa, recombinant activated factor VII; RNAi, ribonucleic acid interference; SAE, serious adverse event; s.c., subcutaneous; TEAE, treatment-emergent adverse event; TFPI, tissue factor pathway inhibitor; TMA, thrombotic microangiopathy; US, United States.

[a]In the dose-finding trial (n = 18), four patients tested positive for ADAs. In the pooled HAVEN clinical trials, 3.5% of patients (14/398) tested positive for antiemicizumab antibodies and <1% (3/398) developed ADAs with neutralizing potential (based on declining pharmacokinetics). One patient from HAVEN 2, who developed an ADA, experienced loss of efficacy after 5 wk of treatment. There was no clinically apparent impact of the presence of ADAs on safety. Two of 88 children in HAVEN 2 developed ADAs with one patient having loss of emicizumab efficacy.[17]

[b]A fatal thrombotic event occurred in a patient with haemophilia A without inhibitors in the Phase III open-label extension study.[21]

The burden imposed by ITI and related difficulties may influence when ITI is initiated, as the timing of initiation could affect the acceptability and feasibility of this treatment from the patient and caregivers' perspectives. However, ITI still remains the first choice and should be initiated as soon as it is feasible. It should also be noted that emicizumab could potentially be administered alongside ITI.[35] A recent case series of seven paediatric inhibitor patients provided the first evidence that concomitant use of ITI and emicizumab prophylaxis (the 'Atlanta' protocol) is feasible,[36] and the safety and efficacy of this approach is being investigated further in observational and prospective studies.

In addition, nonfactor products offer prophylaxis in situations where ITI is delayed (for example, to allow patients and/or caregivers time to prepare psychologically for ITI or for the venous access required for ITI, or while waiting for the inhibitor titre to decrease to <10 Bethesda Units [BU]/mL, as advocated by some treaters). Nonfactor product prophylaxis may also help preserve joints in children treated on-demand with bypassing agents while they wait for ITI. Subcutaneous administration reduces prophylaxis burden by reducing infusion frequency and potentially improving compliance.

In the third scenario, the panel considered adult patients, including older individuals and/or those with comorbidities. The rationale for switching mentioned above also apply here; indeed, older patients with comorbidities (such as high blood pressure and subsequent increased intracranial bleed risk) may have a greater medical need for nonfactor products, especially given the efficacy of prophylaxis with these agents demonstrated in trials.[12,21] However, caution must be advised: patients with haemophilia may develop a greater thrombosis risk as they age and develop comorbidities such as cardiovascular disease, hypertension and hyperlipidaemia.[37,38] Patients with overt, or high risk of, clinical thrombotic problems were excluded from the clinical trials of these novel agents; this may be grounds for exercising caution as there are limited safety data in such individuals. Thrombotic microangiopathy (TMA) and thrombosis were reported in patients receiving emicizumab prophylaxis, although these complications appeared to be restricted to those receiving multiple infusions of higher doses of pd-aPCC for breakthrough bleeds[21] (see Section 2.2). Caution is also recommended when considering treating older patients or those with higher thrombotic risk with fitusiran, which, by suppressing AT production,[12] inhibits the anticoagulation pathway. Specific indications for fitusiran use are reported in the trial protocol. Fitusiran treatment reduced mean maximum AT levels by 70%-89% vs baseline in a phase I dose escalation study,[12] but the study was temporarily halted after a participant without inhibitors suffered a fatal thrombotic event.[14] However, this fatal cerebral sinus thrombosis occurred after repeated infusions of high-dose FVIII for >24 hours, which was advised against in the trial protocol.[39] Although the thrombotic risk with fitusiran is currently anecdotal as evidence is scarce, it may be inadvisable to use treatments that significantly reduce AT in higher-risk individuals. To date, no thromboembolic events have been reported in PwHA or PwHB with or without inhibitors treated in clinical trials with PF-06741086 (marstacimab),[16] an anti-TFPI monoclonal antibody that inhibits the anticoagulant process through their inhibitory effects on TFPI.

Thus, when managing higher-risk patients, including older individuals, a balance must be found between protecting against a potentially higher risk of thrombosis and providing adequate haemostatic coverage to prevent serious (including intracranial) bleeds. It is interesting to note that, even in the context of orthopaedic surgery, the risk of thromboembolism is similar in haemophilia patients and the general population.[40]

In the fourth scenario, the panel considered patients with mild haemophilia and inhibitors. Patients with mild haemophilia do not usually require prophylaxis (with factor-replacement therapy or other agents). However, FVIII levels may drop in these patients, with them becoming more severe phenotypically and experiencing higher bleed rates with attendant need for treatment. Patients with mild haemophilia and low-titre inhibitors are usually managed with higher doses of factor-replacement therapy or prophylaxis but, in the event of inadequate clinical response, they may require bypassing agents or nonfactor products.

2.2 | How should breakthrough bleeds be treated in HwI on emicizumab prophylaxis?

2.2.1 | Consensus

- Emicizumab may be insufficient as monotherapy when breakthrough bleeds occur.
- The adjunct treatment of choice is rFVIIa in patients with high-titre inhibitors (≥5 BU); the standard recommended dose (90 μg/kg) should be used.
- For mild mucosal bleeds, antifibrinolytics such as tranexamic acid may be used alone or with rFVIIa in emicizumab-treated patients.
- FVIII may be used to treat very serious bleeds in patients with a low inhibitor titre (<5 BU) until an anamnestic rise in inhibitor levels (see section 2.3).
- Only consider pd-aPCC for treating bleeds if no alternative is available; only lower doses (<100 U/kg/d or for ≤1 d) should be administered under hospital supervision to monitor for possible TMA or thrombotic events.[5] Avoid dual or sequential therapy with rFVIIa and pd-aPCC in patients receiving emicizumab prophylaxis.

2.2.2 | Rationale/evidence

Despite a reduction in ABR, breakthrough bleeds remain a problem with emicizumab, and possibly other new nonfactor products, as absolute bleed control is not achieved.[17,25] Therefore, it is crucial to determine how best to use these drugs in conjunction with other medications.

Emicizumab mimics FVIII cofactor function; it has a long half-life (28.3-34.4 d) vs replacement clotting factor and increases thrombin generation.[41] Consequently, emicizumab produces a

persistent, low-grade activation of the coagulation system, a key consideration when choosing a bypassing agent to treat breakthrough bleeds. pd-aPCC acts at several points of the coagulation cascade and thus can stimulate prolonged activation of the procoagulant process.[42] Combined administration of pd-aPCC with an emicizumab analogue at clinically relevant doses has been shown to result in excessive thrombin generation—a synergistic effect largely attributable to the emicizumab analogue combining with the FIX (and, to a lesser extent, with the FIXa) found in pd-aPCC.[5,43] Thus, adding pd-aPCC to emicizumab treatment should be avoided if possible.[17] If it is not possible to avoid pd-aPCC, it should be administered at the lowest possible dose for the shortest possible duration. In the phase III HAVEN 1 trial (NCT02622321), five patients on emicizumab prophylaxis who received pd-aPCC (>100 U/kg/d for more than 1 d) for breakthrough bleeds developed TMA or thrombosis; in one patient who developed TMA following treatment with pd-aPCC for rectal haemorrhage, the rectal bleeding eventually proved fatal.[21] No thromboembolic complications occurred in patients receiving emicizumab alone, emicizumab with any dose or duration of rFVIIa, or emicizumab with pd-aPCC given at a dose of <100 U/kg/d or for ≤1 d.[17] Recently, the safety profile of rFVIIa in the context of emicizumab treatment was assessed using all available data from HAVEN 1, 2 and 4: there were no serious adverse events (AEs), TMA cases or thromboembolic events in patients who received rFVIIa to treat breakthrough bleeds while on emicizumab prophylaxis.[44] In a recently published case report, a PwHA with inhibitors on emicizumab prophylaxis experienced a myocardial infarction and pulmonary embolism after administering one dose of rFVIIa to treat an ankle bleed. However, the patient also had a history of prior thrombosis, thrombocytosis, smoking and active infection leading to significant inflammation. Therefore, in the presence of multiple risk factors, concomitant emicizumab and rFVIIa may increase the risk of arterial thrombosis and should therefore be used with caution.[45] A recent editorial outlines the safety concerns associated with emicizumab use, particularly the 13 fatalities (including 11 patients with inhibitors) that may have occurred during compassionate use.[46]

Based on the above observations, rFVIIa should be considered the bypassing agent of choice for treating breakthrough bleeds in emicizumab-treated patients.[17,25] rFVIIa should be used at the recommended dose (90 µg/kg body weight),[47] as combining rFVIIa at a dose equating to 120 µg/kg with an emicizumab analogue led to increased thrombin generation that was still lower than normal. If concomitant use of emicizumab and pd-aPCC is necessary, treatment should be administered in hospital and carefully monitored,[5,6,25] and pd-aPCC should be given at the lowest possible dose for the shortest possible duration needed to control the bleed.[17] Tranexamic acid has been effectively used as haemostatic therapy in patients receiving emicizumab, with no AEs reported,[48] and may be sufficient for mild mucosal bleeds (alone or in conjunction with rFVIIa).[25] It must be highlighted that safety data (particularly in combination with bypassing agents) are product specific and general statements cannot be made for all nonfactor-replacement agents.

Two practical considerations emerge from our recommendation to use rFVIIa for treating breakthrough bleeds. First, patients should maintain a supply of rFVIIa at home; however, monitoring is needed to track its use and to ensure patients are checking rFVIIa expiry dates. Second, bear in mind that patients who are accustomed to s.c. infusions may lose the ability or confidence to administer the iv injections needed to treat bleeds. Clear protocols for bleed treatment and follow-up should be established, and shared care arrangements may also be helpful or necessary.

2.3 | How to perform surgery

2.3.1 | Consensus

- Delay nonurgent, major surgery until more data are available or conduct the surgery in centres with relevant experience in using emicizumab (including its use in conjunction with bypassing agents). Major elective orthopaedic surgeries should be conducted prior to initiating emicizumab, or in experienced centres.[17]
- Patients receiving emicizumab prophylaxis who undergo surgery may require additional haemostatic support.[17] Antifibrinolytics may sufficiently cover oral/dental procedures. When bypassing agents are required as an adjunct bleed-preventative therapy, rFVIIa is recommended. There is no evidence to support using lower rFVIIa doses during surgery in emicizumab-treated patients. pd-aPCC should be considered a second-choice adjunct treatment and administered at low doses with caution.
- FVIII may be effective in treating some surgical bleeds in patients with a low inhibitor titre (<5 BU). In such situations, the laboratory should be proficient at measuring FVIII levels in patients on emicizumab.
- If possible, all major surgery in patients with inhibitors, including in emicizumab-treated patients, should be carried out in a Haemophilia Comprehensive Care Centre.[17]

2.3.2 | Rationale/evidence

Published data on surgeries in emicizumab-treated patients are still limited, but some experience is accumulating from clinical trials[49,50] and case reports.[48,49,51-56] In a recent pooled analysis of four phase III trials (HAVEN 1, 2, 3 and 4), which included PwHA with or without inhibitors undergoing minor or unplanned major surgery while receiving emicizumab prophylaxis,[50] 214 minor surgeries (including dental, placement of central venous access devices, endoscopy, joint and other procedures) were performed in 113 patients, and 19 major surgeries were performed in 19 patients. Most minor surgeries (141; 65.9%) did not require additional haemostatic treatment, and there was no postoperative bleeding in the majority of these cases (128; 90.8%). Seventy-three minor procedures were managed with additional haemostatic support, 64 (87.7%) of which remained free of postoperative bleeding.

Recombinant FVIIa was used in approximately 90.5% of minor procedures in inhibitor patients that required additional haemostatic prophylaxis. The majority of major surgeries (16/19; 84.2%) were performed using haemostatic agents, one of which resulted in a postoperative bleed; no postoperative bleeding occurred in the three major procedures conducted without additional haemostatic treatment. Most major surgeries in inhibitor patients that required additional prophylaxis were managed using rFVIIa (88.9%). There were no deaths, thrombotic events, FVIII inhibitors or unexpected bleeding in any patient.[50]

A number of case series and case reports also describe surgical procedures in inhibitor patients receiving emicizumab prophylaxis, with various management strategies and outcomes. Four of these case reports/series describe major orthopaedic surgeries,[48,52,53,56] two report invasive procedures in paediatric patients,[51,54] and three show that minor procedures conducted under emicizumab prophylaxis do not always require additional haemostatic support.[51,54,55] In these case reports, no patients experienced thrombosis or TMA while receiving additional rFVIIa or FVIII to manage surgery; however, one patient treated with pd-aPCC for a postoperative bleed developed TMA.[55]

Based on these (albeit limited) data, we consider it unlikely for major surgery to be routinely performed without additional haemostatic support in most patients receiving emicizumab prophylaxis, an opinion shared by the UK Haemophilia Centre Doctors' Organisation for orthopaedic procedures.[25] To explore this further, a phase IV trial is underway to investigate minor surgical procedures, without the use of bypassing agent preventative therapy, in patients with HAwI receiving emicizumab prophylaxis (NCT03361137) (Table 1). Meanwhile, until more evidence becomes available, it is prudent to cover surgery with additional haemostatic treatment. The impact of surgery and blood loss on the efficacy of such treatment in patients with HAwI is currently unknown.

We recommend rFVIIa as the adjunct treatment of choice to prevent bleeds for emicizumab-treated inhibitor patients undergoing surgery. The limited evidence currently available suggests that rFVIIa is safe and effective in preventing bleeding during surgery and treating surgical bleeds in emicizumab-treated patients when used at standard doses.[44,49] Lack of response to rFVIIa may necessitate use of pd-aPCC; in this case, the first dose of pd-aPCC should not exceed 50 U/kg and the total daily dose should not exceed 100 U/kg. Patients treated with emicizumab and pd-aPCC should be monitored closely for TMA.[25] In patients with a low inhibitor titre (<5 BU), it may be feasible in some circumstances to use FVIII (rather than bypassing agents) when requiring additional haemostatic support.[48] This would necessitate regular inhibitor testing in patients receiving emicizumab prophylaxis to check for persistent inhibitors. The authors also note that tranexamic acid (as standalone therapy or with FVIII or rFVIIa) may sufficiently treat bleeds associated with oral surgery and other procedures that may cause mucosal bleeds.[25,48]

2.4 | Suitable laboratory assays for measuring new products

2.4.1 | Consensus

- Following emicizumab administration, FVIII replacement can be monitored by chromogenic assays using bovine coagulation factors; limitations include assay availability in laboratories.
- Inhibitor titre should be assessed using a chromogenic Bethesda assay with bovine reagents for FVIII: bovine reagents are insensitive to emicizumab, which was selected to be specific to human FVIII and FIX.
- It is too early to suggest how to monitor nonfactor treatments that are still under development and not yet licensed, but guidelines will be needed for these products in the future.

2.4.2 | Rationale/evidence

Monitoring of emicizumab treatment is not routinely undertaken.[17] There is limited evidence on monitoring emicizumab and much to learn regarding the monitoring of other nonfactor-replacement products currently in development. Emicizumab does not require activation, has no known means of inactivation and may persist in plasma for months after dosing cessation.[17] Together, these factors affect how emicizumab levels and activity are monitored.

Emicizumab is known to affect coagulation laboratory assays that are based on intrinsic clotting by generating overly shortened clotting times.[5,6] Such tests include the activated clotting time, activated partial thromboplastin time (aPTT) and assays based on aPTT, including one-stage aPTT-based clotting assays (Table 2). Emicizumab also interferes with chromogenic FVIII assays that use human coagulation factors, overestimating the haemostatic potential of emicizumab. Therefore, none of these assays should be used to assess FVIII levels or FVIII inhibitor titres.[5,6,17] However, emicizumab does not interfere with chromogenic assays that use bovine coagulation factors, so these assays can be used to monitor endogenous and infused FVIII activity during emicizumab treatment.[5,6,17] Additionally, as emicizumab is not inactivated by FVIII inhibitors, it will interfere with the results of clotting-based Bethesda assays for FVIII inhibitor titres. A chromogenic Bethesda assay using a bovine-based FVIII chromogenic test should therefore be used to measure FVIII inhibitor titres.[5,6,17] Currently, these assays are not available in all laboratories; however, this situation may need to change in light of the recent emicizumab approvals.

The thrombin generation assay (TGA) has also been proposed as a potential method for monitoring combined treatment with emicizumab and bypassing agents, as all result in thrombin generation.[17,57] However, mixed results have been reported.[48,57,58] The TGA is difficult to standardize, and further confirmation of its validity should be sought.

Ultimately, effective monitoring of treatment with nonfactor products will require education about currently available tests, along

TABLE 2 Commonly used coagulation tests and emicizumab treatment[a5,6]

Test results affected by emicizumab	Test results unaffected by emicizumab
• aPTT • Bethesda assays (clotting-based) for FVIII inhibitor titres • One-stage, aPTT-based, single-factor assays • aPTT-based APC-R • Activated clotting time	• Bethesda assays (bovine chromogenic) for FVIII inhibitor titres • TT • One-stage, PT-based, single-factor assays • Chromogenic-based assay with bovine reagents for FVIII • Immuno-based assays (such as ELISA, turbidimetric methods) • Genetic tests of coagulation factors (such as Factor V Leiden, Prothrombin 20210)

Abbreviations: APC-R, activated protein C resistance; aPTT, activated partial thromboplastin time; ELISA, enzyme-linked immunosorbent assay; FVIII, factor VIII; PT, prothrombin time; TT, thrombin time.
[a]Due to the long half-life of emicizumab, the effects on coagulation assays may be observed up to 6 mo after the last dose.

with greater interaction between laboratory staff and physicians to ensure awareness of which products are being administered and which assays are used.

2.5 | Patient-reported outcomes and impact of new treatment options on patient quality of life

2.5.1 | Consensus

- It is crucial to monitor patient-reported treatment outcomes with emicizumab and other new nonfactor products, upon approval. For example, obtaining comprehensive details about bleeding episodes over time (including cause of bleed), as the bleeding phenotype might change.
- Record details about pain, lifestyle changes, joint status and physical activity levels.
- Regular data collection and long-term follow-up are crucial, even if bleed frequency decreases.

2.5.2 | Rationale/evidence

If a patient switches to a nonfactor-replacement product, one might reasonably expect a beneficial impact on bleeding frequency, joint status, physical activity, quality of life (QoL) and treatment burden. These outcome measures should all be assessed to evaluate treatment benefits. Of these, bleed frequency is the most critical, with the greatest repercussions; one should consider bleed number, severity, joint ABR and bleeding in target joints.[59] This latter consideration is important as recurrent bleeds into joints lead to progressive damage and haemophilic arthropathy, especially in patients with inhibitors.[60,61] Long-term follow-up over years is required.

Patients should also record their bleed details, including type and severity, time from previous injection and what precipitated it. While a high proportion of patients (almost 90%) in clinical trials achieved zero bleeds after receiving emicizumab prophylaxis for 73-96 weeks,[62] it is important to emphasize that a target of zero bleeds may not be realistic for all patients in a real-world setting, especially those with chronic arthropathy; it is therefore important to manage expectations accordingly.

Bleeding into joints and muscles causes acute pain and routine assessment of joint health is an important aspect of clinical care.[63] Physiotherapists will play a vital role in assessing joint status, as this is difficult to evaluate outside of clinical trials. As with all therapies, joint pain will be a key outcome measure for patients treated with nonfactor-replacement products; however, pain is a subjective measure.[63]

The nonfactor-replacement products offer the promise of improvements in patient lifestyle. In HAVEN 1, emicizumab-treated patients had significant improvements in health-related QoL and health status vs patients with inhibitors receiving no prophylaxis.[21,64] Effective treatments might encourage increased activity in patients, but there is risk of activity-related bleeding. Physical activity should be measured using a validated tool such as the Haemophilia Activities List (HAL)[65] or the International Physical Activity Questionnaire (IPAQ)[66] so that a 'safe' level of supervised activity can be determined and implemented. Monitoring activity levels in this way is crucial when patients receive treatments (such as emicizumab) that produce persistent haemostatic activity for prolonged periods.

The mental and psychosocial effects of treatment should also be assessed, but both are subjective[59,67] and often difficult to measure: QoL questionnaires can be limited in grasping the mechanisms and processes that lead to different outcomes; there is variability in patients' individual wellbeing and perceptions too,[59,68] such as a patient's feelings towards being able to undertake activities that were previously impossible. Treatment burden, while easier to measure, is still subjective[59]—some patients may find iv infusions problematic, whereas others (particularly older patients) trust this form of administration and are reluctant to switch.

3 | FUTURE TREATMENT OPTIONS FOR PwHB AND INHIBITORS

3.1 | Consensus

- Emicizumab cannot be used in PwHB. Other novel therapies and gene therapy are future treatment options for such patients.[69,70]

3.2 | Rationale/evidence: haemophilia B with inhibitors

Novel, nonfactor products under investigation in PwHB and inhibitors are AT inhibitors (fitusiran), TFPI inhibitors (such as PF-06741086 [Table 1]), activated protein C (APC) inhibitor (novel bioengineered anti-APC serpin) and premature codon suppressors

(relevant for the small number of PwHB who have missense mutations). As these nonfactor products may represent an alternative to ITI and bypassing agents in haemophilia B, it is possible that indications for their use in PwHB with inhibitors might be more generous than those in HAwI.

While both haemophilia A and B display favourable characteristics for gene therapy research (such as reliable quantitative assays to assess efficacy and readily available animal models), haemophilia B has the added advantage of a small *F9* coding sequence, enabling insertion into different gene transfer systems.[71] Research into gene therapy has therefore progressed further for haemophilia B than for haemophilia A. Approaches to gene therapy in haemophilia B include mutation repair, cell-based gene therapy, viral and nonviral gene transfer.[72] Promising results have recently been achieved with FIX-Padua skeletal muscle gene therapy in an inhibitor-prone dog model of haemophilia B.[73] However, as inhibitors are an exclusion criterion for gene therapy clinical trials, there are no clinical data available yet from PwHB and inhibitors.

A word of caution must be offered about gene therapy trials (and trials of any new therapeutic product): patient safety must be prioritized, and physicians should not rush to enrol patients without careful consideration of the benefits and risks involved. Of particular concern for PwHB and inhibitors is that certain types of mutations are at higher risk for developing anaphylaxis and nephrotic syndrome during ITI.[74] This may cause concerns that gene therapy may also induce anaphylactic reactions and nephrotic syndrome as a consequence of restored, prolonged FIX exposure. However, hepatic adeno-associated viral *F9* gene transfer in a murine haemophilia B model restored haemostasis while also supressing cellular antibody production and reducing circulating immunoglobulin G and E to undetectable levels, thus avoiding both anaphylaxis and nephrotic syndrome.[75]

We must also consider that, even if gene therapy becomes a reality one day for PwHB and inhibitors, some may be reluctant to try it. This may be especially true for patients who are already satisfied with weekly dosing or dosing every 2 weeks with extended half-life FIX and for older patients resistant to change.

4 | SUMMARY

These consensus recommendations summarize some of the complex, practical aspects of treatment with nonfactor products in HwI. Emicizumab is currently the only licenced nonfactor therapy, and our recommendations focus on this product. It is our opinion that target candidates for treatment with nonfactor-replacement products fall into four main categories:

- Patients with unsuccessful ITI (no new planned ITI)
- Children with newly developed, high-titre inhibitors, or adults with high-titre inhibitors who have not undergone ITI (eg due to venous access issues or a reluctance to undergo ITI)
- Older adults and/or those with comorbidities
- Patients with mild haemophilia and inhibitors.

It is also our opinion that ITI should be considered in all patients who have developed an inhibitor.

Emicizumab may be insufficient as monotherapy and adjunct therapy may be needed when breakthrough bleeds occur or to prevent bleeds in those undergoing surgery. In these circumstances, rFVIIa (rather than pd-aPCC) is the recommended bypassing agent; this aligns with the emicizumab prescribing information, which advises against pd-aPCC as the first choice of adjunct treatment. Monitoring treatment with nonfactor products is challenging, and it is hoped that ongoing investigations in this area will inform best practice and increase the practicality of their use upon approval. Further, it will be especially important to monitor patient-reported outcomes in those treated with emicizumab or other nonfactor products, with a focus on bleed frequency, joint status, pain and physical activity levels. Emicizumab cannot be used in PwHB and inhibitors, and the future of treatment for these patients may lie in other nonfactor therapies and/or gene therapy.

Although these treatments offer great promise, clear protocols for their use and increased patient education regarding treatment of breakthrough bleeds are urgently needed. Additionally, further research and publication of additional data (including phase IV post-authorization pharmacovigilance studies and real-world evidence in larger populations for emicizumab treatment) are required to assess expected and unexpected outcomes, such as inhibitor development, risk of thrombosis and any other serious AEs.

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