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REVIEW ARTICLE

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Inhibitors in haemophilia A and B: Management of bleeds, inhibitor eradication and strategies for difficult-to-treat patients

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Abstract

The standard therapy for patients with haemophilia is prophylactic treatment with replacement factor VIII (FVIII) or factor IX (FIX). Patients who develop inhibitors against FVIII/FIX face an increased risk of bleeding, and the likelihood of early development of progressive arthropathy, alongside higher treatment-related costs. Bypassing agents can be used to prevent and control bleeding, as well as the recently licensed prophylaxis, emicizumab, but their efficacy is less predictable than that of factor replacement therapy. Antibody eradication, by way of immune tolerance induction (ITI), is still the preferred management strategy for treating patients with inhibitors. This approach is successful in most patients, but some are difficult to tolerise and/or are unresponsive to ITI, and they represent the most complicated patients to treat. However, there are limited clinical data and guidelines available to help guide physicians in formulating the next treatment steps in these patients. This review summarises currently available treatment options for patients with inhibitors, focussing

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on ITI regimens and those ITI strategies that may be used in difficult-to-treat patients. Some alternative, non-ITI approaches for inhibitor management, are also proposed.

KEYWORDS
coagulation disorders, paediatric haematology, quality of life

1 | INTRODUCTION

Haemophilia A and B are rare bleeding disorders caused by a deficiency or lack of clotting factor VIII (FVIII) or factor IX (FIX), respectively. For patients with severe haemophilia (clotting factor <0.01 IU/mL; <1% of normal), standard therapy should be prophylactic treatment with replacement factor FVIII/FIX.[1] The development of neutralising antibodies (inhibitors) against FVIII or FIX is the most serious complication of haemophilia treatment,[2,3] occurring in 20%-30% of patients with severe haemophilia A, 5%-10% of patients with mild-to-moderate haemophilia A, and fewer than 5% of patients with severe haemophilia B.[1] These antibodies render replacement therapy ineffective, with a consequent increase in the risk of serious bleeding and an earlier onset of progressive arthropathy,[3,4] and also higher treatment-related costs.[5] While inhibitors usually develop within the first 20 exposure days and thus are an issue in young patients who receive prophylaxis,[6] inhibitors are also a concern for older patients.[7]

Patients with haemophilia and inhibitors and/or their caregiver(s) report reduced health-related quality of life (QoL) compared with those unaffected by inhibitors,[8,9] and this is particularly apparent as patients grow older.[10] Factors leading to an impaired QoL in patients with inhibitors include frequent bleeds, pain, higher incidences of mobility-related problems, hospitalisations, school and work absenteeism, difficulty maintaining a job[8] and intensive treatment regimens that often require significant time commitments and which can be financially and emotionally demanding for both patients and caregivers.[5,8] High-intensity treatment regimens requiring rigorous adherence can also be challenging and non-adherence can reduce therapy success rates,[8] which further impacts a patient's psychosocial wellbeing. For the caregivers of children with inhibitors, disappointment, isolation and general strain were significant among the reported burdens.[9]

While the recently approved non-factor therapy, emicizumab (Hemlibra®, Roche, Basel, Switzerland) provides new treatment options for patients with haemophilia A and inhibitors against FVIII, the authors do not recommend emicizumab as first-line therapy in these patients (this is discussed in more detail in Section 3.1). The preferred management strategy for patients with haemophilia A who develop high-titre inhibitors is antibody eradication via immune tolerance induction (ITI).[2,3] Bleeding episodes can be treated with bypassing agents[3,11] and potentially with novel haemostatic agents currently in development.[12] The majority of patients with haemophilia A and inhibitors will become "immune tolerant" to FVIII following ITI, with international registries reporting success rates of 51%-79%.[13-16] However, some patients will be difficult to tolerise and/or are unresponsive to first-line ITI, and these patients are the most complicated to treat.[3,17]

ITI may also be attempted in patients with haemophilia B and high-titre FIX inhibitors, but it is utilised less frequently than in those with haemophilia A due to a general lack of experience of its use in haemophilia B and lower overall success rates, as well as concern about anaphylactic reactions and development of nephrotic syndrome.[2,3,13] The lack of data for ITI in patients with haemophilia B and inhibitors means that the optimal approach for achieving successful outcomes in these patients has not been clarified.[2,13]

This review summarises currently available treatment options for patients with inhibitors, starting with the treatment of bleeds and prophylaxis but focussing largely on ITI regimens, including those ITI strategies that can be used in difficult-to-treat patients. We also propose several non-ITI treatment alternatives that may be helpful in managing patients with haemophilia and inhibitors.

2 | MANAGING BLEEDS IN PATIENTS WITH INHIBITORS

Bleeds in patients with low-titre inhibitors can usually be managed by increased doses of FVIII/FIX. For patients with high-titre inhibitors, bypassing agents are used for bleed management, with efficacy rates of 80%-90% following treatment with recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsværd, Denmark) or plasma-derived activated prothrombin complex concentrate (pd-aPCC; FEIBA®, Shire, Lexington, KY, USA).[3,18-20] The FEIBA NovoSeven® Comparative (FENOC) study, which compared the ability of these two agents to treat joint bleeds in patients with haemophilia A and inhibitors, found similar haemostatic efficacy for both products,[20] but neither rFVIIa nor pd-aPCC could predictably achieve haemostasis in all patients or in all bleeds; approximately 30% of patients reported better efficacy with one product over the other.[20] However, it is not possible to predict which product a patient will respond to better.[3] While pd-aPCC has the advantage of a longer half-life vs rFVIIa,[21] it should also be noted that pd-aPCC contains FVIII and FIX, which can result in allergic reactions and anamnestic response in some patients.[3]

Antibody removal by plasmapheresis or immunoadsorption, followed by replacement factor infusion, is a possible option for the management of acute bleeds,[11] but is rarely feasible in clinical practice. In mild forms of haemophilia A, desmopressin (1-deamino-8-D-arginine vasopressin), which enhances endogenous FVIII levels, can be used to treat minor bleeds in patients with low-titre inhibitors in some cases.[22,23]

Managing acute bleeds is especially challenging in older patients with haemophilia and inhibitors, since the presence of age-related

TABLE 1 Frequently used definitions of successful, partially successful, and unsuccessful ITI in patients with haemophilia A with inhibitors, adapted from Benson et al[17]

Success	Partial success	Unsuccessful
• Inhibitor titre <0.6 BU/mL on ≥2 consecutive monthly measurements • FVIII recovery ≥66% of expected values • FVIII half-life ≥6 h after 72-h FVIII washout, and no anamnestic response upon subsequent FVIII exposure	• Reduction in inhibitor titre to ≤5 BU/mL • FVIII recovery <66% of predicted • FVIII half-life <6 h after 72-h FVIII washout associated with clinical response to FVIII therapy, and no increase in inhibitor titre >5 BU over 6 mo of on-demand treatment or 12 mo of prophylaxis	• Not attained defined success or partial success within 33 mo of uninterrupted ITI • Not demonstrated ongoing inhibitor titre reduction ≥20% during each interim, non-overlapping, 6-mo period of uninterrupted ITI, beginning 3 mo after initiation to allow for expected anamnesis (reasonable duration of unsuccessful ITI: minimum 9 mo; maximum 33 mo)

BU, Bethesda units; FVIII, factor VIII; ITI, immune tolerance induction.

comorbidities adds further complications to an already complex clinical scenario.[24]

3 | PROPHYLAXIS IN PATIENTS WITH INHIBITORS

3.1 | Emicizumab

Emicizumab has been recently approved by the US Food and Drug Administration and European Medicines Agency for routine prophylaxis in patients with haemophilia A and FVIII inhibitors who are not currently undergoing ITI and is proving to be an effective prophylactic therapy in these patients. Safety and efficacy in patients receiving ongoing ITI have not yet been established.[25] Emicizumab has a mechanism of action that is not based on replacement or bypass therapy; it is a bispecific monoclonal antibody to activated FIX and factor X, which mimics the cofactor function of FVIII and can be administered subcutaneously.[26,27] Phase III trial data showed that, in patients with haemophilia A and inhibitors, emicizumab prophylaxis was associated with a significant reduction in the annualised bleeding rate compared with no prophylaxis ($P < 0.001$).[26] A good safety profile was reported for emicizumab administered alone or in conjunction with rFVIIa alone. However, in this study, thrombotic microangiopathy and thrombosis (in two participants each) developed following administration of multiple infusions of pd-aPCC for breakthrough bleeds while receiving emicizumab prophylaxis; this resolved after pd-aPCC treatment was stopped.[26] Another trial participant receiving emicizumab developed thrombotic microangiopathy following treatment with pd-aPCC for rectal haemorrhage; however, the rectal bleeding was recurrent and eventually fatal.[26] Synergistic thrombin generation has been reported with aPCC in combination with emicizumab.[28] In light of these observations, recent guidance from the UK Haemophilia Centre Doctors' Organisation (UKHCDO) recommends rFVIIa as a first-line treatment for breakthrough bleeds in patients on emicizumab prophylaxis, with close observation for thrombosis. While pd-aPCC can be used if there is no response to rFVIIa, or if other options (such as FVIII) are not available or appropriate, treatment should be administered in hospital with careful monitoring.[25] In addition to the above fatality, a further four deaths have subsequently been reported in adults treated with emicizumab, one of whom was being treated in the US expanded access programme and three under compassionate use requests.[29] As with the death during the phase III trial, in all four of these instances, the treating physician considered that the cause was unrelated to emicizumab.[29]

While emicizumab prophylaxis provides an alternative treatment option for patients with haemophilia A and inhibitors, in general, the authors do not recommend that emicizumab be considered a first-line therapy but rather as a rescue treatment for patients with persistent inhibitors. Most patients will eventually be tolerised via ITI and avoiding ITI would necessitate lifelong treatment with emicizumab and bypassing agents, which may not be cost-effective. Furthermore, patients on emicizumab will experience breakthrough bleeds, and bypassing therapy will not be as effective as factor replacement in a tolerised patient. Concomitant use of emicizumab and a bypassing agent may also increase the risk of adverse events (AEs). The authors recommend considering emicizumab prophylaxis in patients who wish to delay ITI to allow the inhibitor titre to fall to <10 Bethesda units (BU)/mL, in very young patients who find daily infusions burdensome, those with poor venous access and/or poor compliance, or those who have not responded to previous courses of ITI. In such patients, emicizumab prophylaxis will be a treatment option instead of a bypassing agent.

3.2 | Bypassing agents

Prophylaxis with bypassing agents has been shown to reduce bleeding events, prevent or delay the development of target joints and arthropathy, as well as to delay the progression of existing joint disease in certain patients, despite lower efficacy compared with FVIII prophylaxis in patients without inhibitors.[30,31] The potential benefits of prophylaxis in preventing arthropathy are particularly relevant for children with unaffected joints undergoing ITI.[31]

Few guidelines on prophylactic use of bypassing agents exist, and those available were published before the approval of emicizumab. Prophylaxis with bypassing agents may be a suitable choice before or during ITI, with the International workshop on ITI, Spanish consensus guidelines, and the UKHCDO guidelines all recommending rFVIIa as the prophylactic agent of choice prior to ITI.[2,30,31] During

ITI, and for those not already undergoing ITI, the guidelines recommend prophylactic use of either pd-aPCC or rFVIIa.[2,30,31] However, it must be noted that rFVIIa and pd-aPCC prophylaxis are not licenced in all countries. Further, the use of bypassing therapy as prophylaxis should be balanced against the inconvenience of administration, the potential (low) risk of thrombosis and cost-effectiveness.[30]

4 | IMMUNE TOLERANCE INDUCTION

4.1 | Defining the outcome of ITI

It is important to establish firm definitions not only of ITI success, but also when treatment has not succeeded. Widely adopted definitions of successful, partially successful, and unsuccessful ITI for patients with haemophilia A and inhibitors have been published previously (Table 1).[17] The International workshop on ITI published many of these definitions, which are still relevant to clinical practice.[2] With these definitions, it advised that an ITI regimen should have a minimum duration of 9 months and a maximum duration of 33 months, before a decision should be taken regarding the success of the treatment.[2] Indeed, defining unsuccessful ITI is more of a challenge than characterising successful or partially successful ITI. The accepted definition of unsuccessful ITI for patients with haemophilia A and inhibitors (Table 1) does not allow for improvement in the clinical phenotype.[17,32] A survey designed to develop a consensus definition of unsuccessful ITI for Australian clinical practice identified clinical outcomes as important factors for assessing ITI response, leading to the conclusion that a reduction in bleeding symptoms alone may be sufficient to justify continuing ITI.[32]

The UKHCDO has also considered these issues and, in their guidelines on the management of inhibitors, propose that a suitable criterion for defining tolerance and restoration of normal FVIII pharmacokinetics (PK) is a FVIII elimination half-life of >7 hours.[31] No similar criterion is proposed for defining tolerance in haemophilia B due to the uncertainty of normal FIX half-life.[31] To avoid the difficulties in measuring FVIII half-life in routine clinical practice, the UK guidelines propose a pragmatic and clinically relevant surrogate measure of normal FVIII PK as a FVIII level of ≥1 IU/dL at 48 hours in a patient receiving standard prophylaxis (20-50 IU/kg on alternate days).[31]

4.2 | Conventional methods for ITI

The conventional methods for ITI include the "Bonn high-dose" regimen or variant protocols[33,34] and the "Van Creveld Dutch low-dose" regimen, or variant protocols[35] (Table 2).[17] In difficult-to-treat cases (see section 4.4), the Malmö protocol is an alternative option (Table 2).[36] The pivotal International Immune Tolerance (I-IT) study, which randomised patients to low-dose (50 IU/kg FVIII, three times a week) or high-dose (200 IU/kg FVIII, daily) regimens, lacked statistical power to show therapeutic equivalence.[37] The FVIII dose did not affect success rate at the end of the study period, although patients receiving a high dose had a significantly shorter time to negative inhibitor titre.[37] Furthermore, a significantly greater number of bleeds was observed in the low-dose arm.[37]

TABLE 2 Summary of the main ITI protocols for patients with haemophilia, from Benson et al[17]

The Bonn protocol • High-dose regimen that includes a bypassing agent • FVIII ~100-150 U/kg BID • pd-aPCC 50-100 U/kg BID • Reported success rate, 92%-100% • Median time to success: 14 mo
The van Creveld (Dutch) protocol • Lower-dose/adaptive dosing of FVIII: neutralising dose and tolerising dose • FVIII 25-50 IU/kg BID for 1-2 wks, then 25 IU/kg every other day • Reported success rate: 61%-88% • Median time to success: 1-12 mo
The Malmö protocol (option for use in difficult-to-treat patients) • High-dose FVIII plus immunomodulation (adsorption and suppression) • Cyclophosphamide 12-15 mg/kg IV daily for 2 days, then 2-3 mg/kg PO daily for 8-10 days • FVIII to achieve a 40%-100% FVIII level, followed by FVIII infusion every 8-12 h to achieve a 30%-80% FVIII level • IVIG 2.5-5 g IV immediately after the first FVIII infusion, followed by 0.4 g/kg daily on days 4-8 • Reported success rate, 59%-82% • Median time to success: 1 mo

BID, twice daily; FVIII, factor VIII; ITI, immune tolerance induction; IV, intravenous; IVIG, intravenous immunoglobulin; pd-aPCC, plasma-derived activated prothrombin complex concentrate; PO, by mouth.

Initially, all ITI protocols utilised plasma-derived factor concentrate. However, with the advent of monoclonal antibody-purified and recombinant factor concentrates, there is now much discussion regarding product type (see next section). Furthermore, although the first ITI protocol was published in the 1970s, the optimal regimen has yet to be defined, partly because clinical studies do not necessarily involve similar patient cohorts and therefore cannot be compared directly.

In the event that ITI is successful and tolerance achieved, the authors recommend long-term continuous prophylaxis, to help maintain tolerance and to avoid rapid changes in dose.

4.3 | Predictors of outcome of conventional ITI

Reports on ITI outcomes collected in several international registries, albeit not always in agreement, have enabled the identification of numerous treatment- and patient-related factors that are predictive of ITI outcome.[17,38] Treatment-related factors that may influence ITI outcome include inhibitor titre at ITI onset, the time elapsed between inhibitor diagnosis and initiating ITI, historical peak inhibitor titre, and peak inhibitor titre during ITI (Table 3). An inhibitor titre of <10 BU/mL at ITI onset is recognised as one of the main determinants of ITI outcome, positively affecting both the likelihood of success and the time taken to achieve success.[2,13-16,38,39] Although the usual recommendation is to delay ITI until the inhibitor titre is <10 BU/mL, but preferably within 2 years of inhibitor onset,[3] prompt ITI should always be considered as a potential therapeutic option, regardless of current inhibitor titre, particularly in patients with frequent and/or severe bleeds.[2,16,31,38,40]

TABLE 3 Potential predictors of outcome of conventional ITI

Potential predictor	Evidence
Treatment-related factors	
Inhibitor titre <10 BU/mL at ITI onset	Supportive: • An inhibitor titre of <10 BU/mL at ITI onset has been shown to positively affect both the likelihood of success and the time taken to achieve success in a number of studies[2,13-16,38,39,41] Against: • Successful ITI was achieved in 13 patients with an inhibitor titre ≥10 BU/mL when initiated within 1 mo of inhibitor detection[40]
Time between inhibitor diagnosis and initiating ITI ≤5 yrs	Supportive: • Registry data, including those from the NAITR and the International IT Registry, found a significant association between achieving tolerance and the time elapsed between inhibitor diagnosis and ITI initiation, with improved outcomes for patients treated within 5 years of inhibitor detection[13,16] Against: • Data from the German registry show that the time interval between inhibitor detection and the start of ITI did not have a significant effect on ITI success[15]
Historical peak inhibitor titre of <200 BU/mL	Supportive: • According to registry data (including those from the Italian PROFIT Registry, the NAITR, the International IT Registry, and the I-IT Study), a historical peak inhibitor titre of <200 BU/mL is associated with a successful ITI outcome[16,37,38]
Low peak inhibitor titre during ITI	Supportive: • An inverse relationship between peak titre on ITI and a successful ITI outcome has been reported[37,38]
Factor dose	Supportive of low dose: • The NAITR found an inverse correlation between daily dose and success rate[13] Supportive of high dose: • The International IT Registry reported improved outcomes with high-dose FVIII product[16] No effect: • The I-IT study found that dose did not affect success rates, although patients on a high FVIII dose had a significantly shorter time to negative inhibitor titre[37]
Product	Supportive of monoclonally purified and rFVIII products: • High ITI success rates (up to 91%) are reported for patients treated with monoclonal and rFVIII concentrates[39,42-44] Supportive of vWF-containing products: • vWF has been speculated to modulate FVIII immunogenicity,[45] and some studies indicate that pd concentrates that contain vWF increase the likelihood of success when compared with pure FVIII concentrates[46,47] No effect: • Data from the International IT Registry and NAITR, as well as a meta-analysis of several studies, show that pd and rFVIII concentrate have similar outcomes when used for ITI[2,13,16,48]
Patient-related factors	
Young age at start of ITI	Supportive: • In the International IT Registry, young age at treatment start positively affected outcome ($P < 0.001$),[16] and the NAITR observed a trend towards a younger mean age in the successful group[13] Against: • The Spanish Registry reported that older patients achieved better results[14] No effect: • No correlation between age at ITI start and ITI outcome was observed in the German registry, the Grifols-ITI Study, or a European study of retrospective data from 22 centres in Italy, Germany and Spain[15,46,49]
Ethnicity	Supportive: • A retrospective, single-centre analysis reported a significantly lower ITI success rate among African Americans (58% vs 92% in non-African Americans); however, the African American patients had higher pre-ITI inhibitor titres[50] No effect: • No difference in success of ITI outcome between patients of different ethnicities was seen in the NAITR and I-IT Study, although it is worth noting that only 8% of patients in the I-IT study were African Americans[13,37]
FVIII genotype	Supportive: • Analysis of data from the Italian PROFIT Registry showed that patients carrying FVIII mutations associated with a high risk of inhibitor development had significantly worse outcomes than patients with lower-risk mutations[51] • A link between "high-risk" FVIII mutations and worse ITI outcome was also reported for two patients with an intron 22 inversion, who had a considerably longer duration to ITI success compared to patients with other mutation types[52] No effect: • A study showed that the FVIII mutation type did not affect the chance of achieving successful ITI[39]

BU, Bethesda units; FVIII, factor VIII; I-IT Study, International Immune Tolerance Study; ITI, immune tolerance induction; NAITR, North American Immune Tolerance Registry; pd, plasma-derived; PROFIT, PROgnostic Factors in Immune Tolerance; rFVIII, recombinant factor VIII; vWF, von Willebrand factor

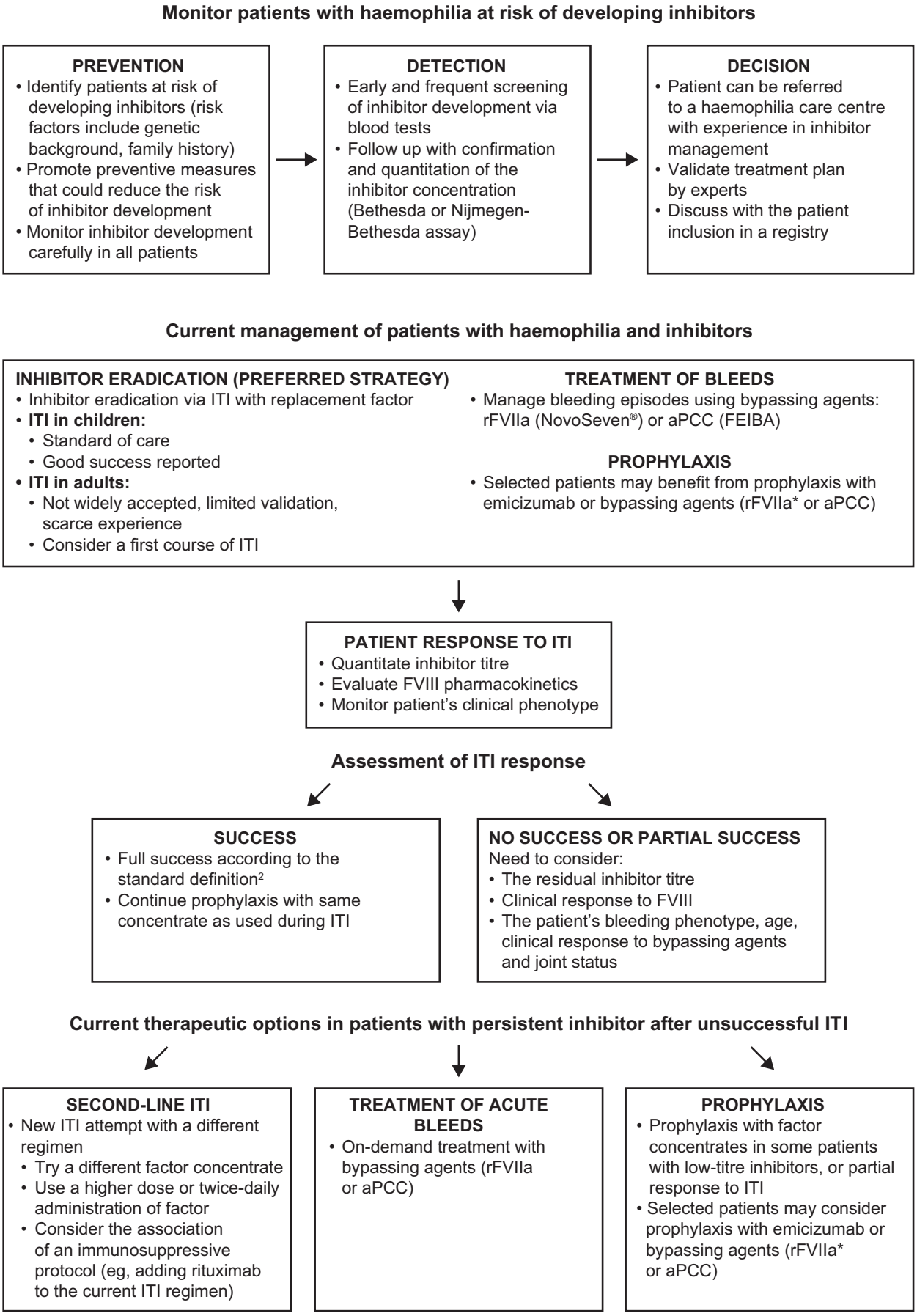
Monitor patients with haemophilia at risk of developing inhibitors
PREVENTION
• Identify patients at risk of developing inhibitors (risk factors include genetic background, family history)
• Promote preventive measures that could reduce the risk of inhibitor development
• Monitor inhibitor development carefully in all patients
DETECTION
• Early and frequent screening of inhibitor development via blood tests
• Follow up with confirmation and quantitation of the inhibitor concentration (Bethesda or Nijmegen-Bethesda assay)
DECISION
• Patient can be referred to a haemophilia care centre with experience in inhibitor management
• Validate treatment plan by experts
• Discuss with the patient inclusion in a registry
Current management of patients with haemophilia and inhibitors
INHIBITOR ERADICATION (PREFERRED STRATEGY)
• Inhibitor eradication via ITI with replacement factor
• ITI in children:
• Standard of care
• Good success reported
• ITI in adults:
• Not widely accepted, limited validation, scarce experience
• Consider a first course of ITI
TREATMENT OF BLEEDS
• Manage bleeding episodes using bypassing agents: rFVIIa (NovoSeven®) or aPCC (FEIBA)
PROPHYLAXIS
• Selected patients may benefit from prophylaxis with emicizumab or bypassing agents (rFVIIa* or aPCC)
PATIENT RESPONSE TO ITI
• Quantitate inhibitor titre
• Evaluate FVIII pharmacokinetics
• Monitor patient's clinical phenotype
Assessment of ITI response
SUCCESS
• Full success according to the standard definition2
• Continue prophylaxis with same concentrate as used during ITI
NO SUCCESS OR PARTIAL SUCCESS
Need to consider:
• The residual inhibitor titre
• Clinical response to FVIII
• The patient's bleeding phenotype, age, clinical response to bypassing agents and joint status
Current therapeutic options in patients with persistent inhibitor after unsuccessful ITI
SECOND-LINE ITI
• New ITI attempt with a different regimen
• Try a different factor concentrate
• Use a higher dose or twice-daily administration of factor
• Consider the association of an immunosuppressive protocol (eg, adding rituximab to the current ITI regimen)
TREATMENT OF ACUTE BLEEDS
• On-demand treatment with bypassing agents (rFVIIa or aPCC)
PROPHYLAXIS
• Prophylaxis with factor concentrates in some patients with low-titre inhibitors, or partial response to ITI
• Selected patients may consider prophylaxis with emicizumab or bypassing agents (rFVIIa* or aPCC)

FIGURE 1 Algorithm for the management of patients with inhibitors, including initial inhibitor prevention approaches, assessment of ITI response, and therapeutic options in patients with a persistent inhibitor after ITI. For more information on inhibitor prevention and detection strategies, please see reviews by Kempton and White, and Coppola et al[11,88] *Please note that rFVIIa is not licenced for prophylaxis in all countries. aPCC, activated prothrombin complex concentrate; FVIII, Factor VIII; ITI, immune tolerance induction; rFVIIa, recombinant activated factor VI

The impact of replacement factor dose and product on ITI outcome is currently uncertain, with conflicting and variable results preventing definitive conclusions being drawn about which dose and product are superior (Table 3); however, data suggest that in poor-risk patients, high-dose regimens are probably more effective.[31,38]

Among patient-related factors, the effect of age at ITI start, patient ethnicity and FVIII genotype have been investigated as potential predictive factors for ITI outcome (Table 3). The impact of age at the start of ITI remains unclear,[13-16,41,49] and there are limited data on the effect of ethnicity on ITI outcome.[13,37,50] Similarly, few studies have investigated the effect of FVIII mutation type on ITI outcome,[39,51,52] and large cohort studies, in which other risk factors can be taken into account, are needed to assess the impact of genotype.

4.4 | ITI strategies for difficult-to-treat patients

An algorithm to assist the management of patients with inhibitors is shown in Figure 1.

4.4.1 | The general patient unresponsive to first-line ITI

In the event of ITI not succeeding using a low- or high-dose regimen of 100-150 IU/kg/d, the authors recommend a further attempt using an increased dose (usually 200 IU/kg/d) of the same product; if venous access allows, administer twice per day. Alternatively, a different factor concentrate can be tried (either at a dose similar to the initial regimen, or at an increased dose). If ITI was initiated with a monoclonal or recombinant product, trying a von Willebrand Factor (vWF)-containing concentrate may improve the chance of success.[2] While the benefits of vWF-containing concentrate in first-line ITI remain debatable (as discussed earlier), successful tolerisation has been reported in patients switching to second-line ITI with a vWF-containing concentrate after being unresponsive to first-line ITI with a high-purity product.[46,47]

As an alternative second-line approach, the authors suggest continuing to administer ITI and adding a further intervention, such as an immunosuppressive agent. Although originally included in the Malmö protocol, the benefit of immunosuppressive agents when added to a standard ITI regimen has not been proven.[2,3,13,36] More recently, however, positive results are being reported with the immunosuppressive agent, rituximab. This is an anti-CD20 antibody that, via rapid depletion of B lymphocytes, is hypothesised to facilitate the induction of immune tolerance in resistant inhibitor cases.[53] While rituximab has primarily shown promise in the treatment of inhibitors associated with acquired haemophilia, a number of case studies in patients with congenital haemophilia and inhibitors unresponsive to ITI have also shown some success.[54-57] In these examples, all successful cases utilised rituximab concomitantly with high-dose FVIII (100 or 200 IU/kg/d) or a Malmö regimen, except for one case where FVIII was administered at a dose of 30 IU/kg/3 times per week.[54-57] For example, a study including data from all 23 comprehensive haemophilia centres in the United Kingdom reported an overall response in 7/15 (47%) cases that had previously experienced at least one round of unsuccessful ITI.[55] In another study, four children with severe haemophilia A and one adult with mild haemophilia A were treated with rituximab.[54] In three patients, the inhibitors disappeared, although FVIII PK did not completely normalise in two patients.[54] It is important to note that information on the long-term safety of rituximab is still lacking and this has raised concerns regarding its use, particularly in children.[53]

4.4.2 | Adults and older patients with inhibitors

There is resistance, by both patients and physicians, to initiate ITI in adults with haemophilia and inhibitors, mainly related to the perceived poor prognosis, demanding treatment regimens and high costs.[58] However, as discussed above, age at ITI initiation should be considered in a larger framework of putative prognostic factors,[58] because older age when starting ITI may not adversely affect the outcome in adult patients with recent-onset inhibitors.[49] In a retrospective observational study of nine patients with severe or moderately severe (≤2% FVIII activity) haemophilia and long-standing inhibitors (4-31 yrs) who underwent late ITI utilising recombinant FVIII products (regimens ranged from 50 IU/kg/3 times per week to 100 IU/kg/daily), seven achieved either partial or full success.[59] Similarly, in another study, 11 of 12 adult patients (<2% FVIII activity), with >24 months between inhibitor diagnosis and ITI, achieved either complete or partial success using a single vWF-containing plasma-derived FVIII (pdFVIII) product.[49]

Although ITI is associated with high costs in adults, a study investigating the lifetime cost of ITI started in childhood vs prophylaxis and on-demand treatment with bypassing agents found that, while initial costs of ITI were high, long-term ITI was no more expensive than other therapies to which it was compared.[60]

In the authors' view, the current data suggest that a course of conventional ITI may be justified in selected adults; however, the likelihood of success and long-term benefits need to be weighed against the cost (both financial and to the patient's QoL). In the light of this, the decision to initiate ITI should be taken by both the physician and the patient, with good support available for the patient. This is particularly necessary in those with long-standing inhibitors. Triggers to initiate late ITI include poor QoL, frequent/severe bleeds poorly controlled and upcoming surgery.[58] In the event that ITI is unsuccessful, careful consideration must be made of the costs and the impact of second-line therapy. With little in the way of

evidence-based guidelines, the management of older patients with haemophilia and inhibitors remains a challenge for haematologists; clinical experience plays a major role in decision making.[24]

4.4.3 | Patients with predictors of non-response

It is the authors' opinion that ITI should be considered for all patients with haemophilia A and inhibitors, even those with characteristics recognised as being predictive of a poor response. For example, favourable response rates were reported in a retrospective analysis of data for children and adults with haemophilia A (<2% FVIII activity) and inhibitors, many of whom had poor prognostic characteristics.[41] Of the patients who underwent primary ITI (n = 41) or rescue ITI (n = 19), 36 of the 45 (80%) of patients who had one or more predictors of poor response to ITI achieved complete or partial success.[41] Furthermore, among the 23 patients with three or more predictors of poor response to ITI, 19 (83%) achieved success (complete: n = 10; partial: n = 9).[41]

Good success rates with a high-dose ITI protocol in patients with characteristics predictive of a poor response to ITI have also been observed in data from the International Immune Tolerance Registry, the North American Immune Tolerance Registry (NAITR) and from two German studies.[61] Success in this patient subgroup appeared to be influenced by the dose and type of concentrate used, with an apparent advantage for high-dose ITI using vWF-containing pdFVIII concentrates over recombinant or vWF-free concentrates.[61] An interim report from the Observational ITI research programme has also shown a high ITI success rate using pdFVIII/vWF product in patients with at least one predictor for poor response to ITI.[62] However, in a meta-analysis involving 13 studies comprising 382 patients, no difference was found in the proportion of patients achieving successful ITI when treated with FVIII concentrates either containing or devoid of vWF.[48]

4.4.4 | Mild haemophilia A

The management of FVIII inhibitors in patients with mild haemophilia A is a challenge due to the older age at onset and seeming lower effectiveness of conventional ITI.[63-65] Nevertheless, in the INSIGHT study (International Study on Etiology of Inhibitors in Patients with a Moderate or Mild Form of Hemophilia A, Influences of Immuno-Genetic & Hemophilia Treatment Factor), which included 101 non-severe patients with haemophilia A and inhibitors, inhibitors disappeared in the majority of patients (72/101; 72%), either spontaneously (51/73; 70%), or after eradication treatment (21/28; 75%).[66] In patients with mild haemophilia A, FVIII inhibitors may share features with FVIII autoantibodies that occur commonly in acquired haemophilia A, and this may explain why immunosuppressive therapy can be effective in reducing the inhibitor titre in some patients.[63,64,67,68]

4.4.5 | Haemophilia B

ITI is less successful in patients with haemophilia B and inhibitors than in those with haemophilia A and inhibitors; indeed, haemophilia B is in itself a poor prognostic indicator of ITI success.[3] Patients with haemophilia B in the NAITR had a success rate of about 30% after ITI with FIX concentrate, and adverse reactions to therapy (including allergic reactions and nephrotic syndrome) were approximately 10 times higher than for patients with haemophilia A.[13] Attempting ITI in patients with FIX inhibitors must therefore be considered very carefully, taking into account the high risk of adverse reactions and the relatively low likelihood of success.[2] One approach that has shown some success is the use of immunosuppressive agents in patients with haemophilia B and inhibitors.[69-71] Indeed, the Malmö centre reported success in six of seven (86%) cases of severe haemophilia B treated according to the Malmö Treatment protocol.[72] Additionally, Beutel and colleagues describe treatment of an 11-year-old patient with a history of allergic reactions to FIX and to pd-aPCC; success was achieved using combined immune-modulating therapy (rituximab, mycophenolate mofetil, dexamethasone, and intravenous immunoglobulins) and high-dose FIX.[69] Following re-emergence of FIX inhibitors 7 years later, this patient was again effectively treated using the same regimen.[73]

4.5 | Managing the psychosocial impact of unsuccessful ITI

In the light of the psychosocial burden imposed on patients and caregivers by inhibitors and their management, psychologists should be included in any comprehensive care team alongside physicians, nurses, social workers, and physical and occupational therapists.[8,11] This ensures that treatment plans encompass both physical and psychosocial evaluations, as well as intervention strategies.[8,11] To improve QoL, symptoms of mental health problems, low self-esteem, low coping skills, depression, anxiety, and substance abuse should be monitored.[8] Some psychosocial issues can be alleviated through self-care, helping the patient correctly identify feelings, teaching anger management techniques, encouraging social contact with peers (for both the patient and the caregiver), as well as providing assistance to improve communication with family and the medical team.[8] Ongoing psychosocial care for both the patient and the caregiver is recommended to maintain an attitude of hope for the future, deal with feelings of guilt, and ensure that adequate educational assistance is available.[8,9] For this reason, psychosocial assessments before and after treatment are as vital as physical assessments. It is also important to recognise that use of the term "failed ITI" may have strong negative connotations and it may be better to use the term "unsuccessful ITI".

5 | ALTERNATIVE NON-ITI TREATMENT APPROACHES FOR PATIENTS WITH INHIBITORS

Treatments for patients with inhibitors continue to be investigated. Prophylaxis with bypassing agents may be an appropriate treatment option for some patients who are unresponsive to ITI[30,31]; sequential

or concomitant therapy with rFVIIa and pd-aPCC might be helpful in difficult-to-treat patients for whom monotherapy with either agent is ineffective.[74,75] One study showed that a combination of low-dose rFVIIa (30-70 μg/kg) and pd-aPCC (20-30 IU/kg) achieved bleeding control in over 400 bleeding episodes in five patients with high-titre inhibitors, with no thromboembolic or other AEs.[74] Clinical data are limited, and more substantial, well-controlled studies evaluating this approach are needed. Combined use of the two agents should only be carried out in the inpatient setting that has experience of this treatment, along with careful monitoring.

Another form of combination therapy involves the administration of FVIII with either rFVIIa or pd-aPCC. An in vitro study using plasma from patients with high-titre inhibitors demonstrated that the addition of FVIII enhanced the haemostatic effect of both bypassing agents; pd-aPCC combined with FVIII had a synergistic effect on thrombin formation, whereas rFVIIa combined with FVIII had an additive effect.[76]

A new FVIII agent for replacement therapy, recombinant B-domain deleted porcine FVIII (OBI-1), demonstrated efficacy and safety for the treatment of bleeding episodes in patients with acquired haemophilia A in phase II/III studies and in patients with congenital haemophilia A in a phase II study.[77,78] A recombinant fusion protein linking rFVIIa with albumin (rVIIa-FP), a new bypassing agent in clinical development with extended half-life,[12,79] showed good tolerability in 40 healthy males in a phase I study.[79]

In addition to the recently approved emicizumab, other therapeutics whose mechanism of action is not based on replacement or bypass therapy are under development for patients with haemophilia A or B. As with emicizumab, potential benefits of these other non-factor therapies include improved compliance due to more convenient subcutaneous (rather than intravenous) administration. Promising early results have been demonstrated with concizumab, a humanised monoclonal antibody targeting anti-tissue factor pathway inhibitor (TFPI)[12]: there were no serious AEs in concizumab-treated patients with haemophilia A or B; improved thrombin generation was observed in patients with haemophilia A and B and in plasma samples from patients with haemophilia A and inhibitors.[80,81] Two other monoclonal antibodies targeting TFPI (BAY 1093884 and PF-06741086) are in development. The PK and pharmacodynamics have been investigated in animal and/or in vitro models;[82-84] phase I (BAY 1093884; NCT03481946 and NCT02571569) and phase II (PF-06741086; NCT02974855 and NCT03363321) clinical studies are ongoing. Another novel agent currently under investigation is fitusiran (ALN-AT3), a synthetic ribonucleic acid interference therapeutic that suppresses antithrombin generation, thereby restoring balance in haemostasis.[85] In a phase I dose-escalation study, a dose-dependent mean maximum antithrombin reduction of 70%-89% from baseline was observed in fitusiran-treated patients, although a participant in the phase II open-label extension trial suffered a fatal thrombotic event.[86,87] Two phase III trials investigating efficacy and safety of fitusiran in patients with haemophilia A or B with/without inhibitors (NCT03417102 and NCT03417245, respectively) are currently recruiting patients. Concizumab and fitusiran are being investigated for prophylactic use in patients with inhibitors using subcutaneous administration.[12,80] This would circumvent the need for venous access, which can be problematic for treatments requiring regular infusions, such as ITI and prophylaxis.

While eradication of inhibitors will likely remain the first priority in inhibitor patients, the non-ITI therapies described here offer promising alternatives as they have the ability to improve haemostasis in the presence of inhibitors, despite differing modes of action.[12] These molecules could provide more options for patients with inhibitors for on-demand or surgical treatment (OBI-1 and rVIIa-FP), as well as prophylaxis (emicizumab, concizumab, and fitusiran). However, it is important to be aware of the potential limitations and side effects of these new agents, such as thrombotic complications.

6 | CONCLUSIONS

ITI is an effective but highly demanding approach to eradicate inhibitors in patients with haemophilia. While evidence-based guidelines and consensus recommendations are valuable, clinical experience continues to play a major role. This is especially the case when managing difficult-to-treat patients, such as those who are unresponsive to first-line ITI, older patients, and those with mild haemophilia A, haemophilia B, or predictors of poor response. Acute bleeds in patients unresponsive to ITI can be treated with on-demand haemostatic therapy, such as bypassing agents. Furthermore, prophylaxis with bypassing agents or, in haemophilia A, with emicizumab may be effective for patients not currently receiving ITI, including those in whom ITI has previously been unsuccessful. The inability to achieve successful ITI in 20%-40% of patients, the high costs of treatment, and the challenges of inhibitor management in both children and adults highlight the expectations from the new prophylactic agents and the need for innovative strategies for achieving immune tolerance.

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CONFLICT OF INTEREST

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