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SPECIAL REPORT



## Key questions in the new hemophilia era: update on concomitant use of FVIII and emicizumab in hemophilia A patients with inhibitors

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### ABSTRACT

**Introduction:** Immune tolerance induction (ITI) is the primary therapeutic strategy and only proven method to eradicate inhibitors to coagulation factor VIII (FVIII) in hemophilia A. Emicizumab, a humanized bispecific monoclonal antibody that mimics the function of activated FVIII, has expanded options to treat hemophilia A. The availability of emicizumab necessitates a revisit of recommendations for managing patients with inhibitors.

**Areas covered:** Current evidence is reviewed about the concomitant use of emicizumab and FVIII concentrates during and after ITI. Areas where data are lacking are highlighted and ongoing studies designed to address these issues are described.

**Expert opinion:** Inhibitor eradication remains a desirable goal. All patients with inhibitors should be offered at least one attempt at ITI. Emicizumab monotherapy is an option for inhibitor patients who are not candidates for ITI. Evidence is emerging about the use of emicizumab during ITI to prevent bleeds. Studies are currently addressing the safety, efficacy, and feasibility of concomitant emicizumab and FVIII in ITI. As evidence regarding the risk of inhibitor recurrence and need for continued FVIII to maintain immune tolerance post-ITI is limited, the role of emicizumab alone or in combination with FVIII after ITI is the subject of an upcoming study.

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Hemophilia A; inhibitor; immune tolerance induction; FVIII; emicizumab

## 1. Introduction

The development of alloantibodies (inhibitors) to infused coagulation factor VIII (FVIII) continues to be the most frequent and serious complication in hemophilia management [1]. Inhibitors to FVIII develop in about 30% of previously untreated patients (PUPs) with severe hemophilia A [2–4], usually within the first 10–20 exposure days [5], hence, very early in life (average age of 2–3 years). Immune tolerance induction (ITI) therapy is the only proven method to achieve inhibitor eradication in hemophilia A, although success rates vary from 60 to 80% [6]. Major disadvantages of ITI are its considerable treatment burden (particularly because venous access is difficult in young children) and high initial cost. Nevertheless, if successful, ITI improves patients' health status and long-term quality of life while reducing treatment costs over the longer term.

Until recently, treatment options for hemophilia A were relatively straightforward. Patients with severe hemophilia A and no inhibitor were generally treated prophylactically with FVIII. In patients with severe hemophilia A who developed high-titer inhibitors, attempting eradication (despite its burden and expense) as a means of reverting to a non-inhibitor state was deemed an absolute necessity. The reasoning behind this approach was that, whereas bypassing agents

(recombinant activated factor VII [rFVIIa] or factor eight inhibitor bypassing activity [FEIBA]) are effective for on-demand treatment of bleeds, they are not as effective or convenient as FVIII prophylaxis in patients without inhibitors. Clinicians recognized that, in the absence of eradication, the lifelong presence of a high-titer inhibitor would result in greater long-term patient morbidity and mortality given the lower effectiveness of bypassing agent prophylaxis at preventing bleeds, and much higher lifelong treatment costs given the high costs of bypassing agents. Thus, the norm when managing patients with hemophilia A and inhibitors was to attempt ITI, often repeatedly.

The introduction of emicizumab (Hemlibra®), a humanized bispecific monoclonal antibody that mimics the cofactor function of activated FVIII [7], has ushered in a new era in hemophilia management. The HAVEN studies showed that emicizumab prophylaxis was highly effective at preventing bleeding in patients with (and without) inhibitors [8–11]. With emicizumab available, and other treatment options in the therapeutic pipeline, the need for inhibitor eradication has become less certain. The availability of emicizumab (the first licensed non-factor replacement therapy) is forcing the hemophilia community to establish a 'new normal' when managing patients with severe hemophilia A and inhibitors.

### Article highlights

- Eradication of inhibitors to coagulation factor VIII (FVIII) remains a desirable goal. All patients with hemophilia A and inhibitors should be offered at least one attempt at immune tolerance induction (ITI). Emicizumab monotherapy is an option for inhibitor patients who must delay or are unable/unwilling to undergo ITI or those who fail ITI.
- Evidence is emerging about the use of emicizumab to prevent bleeds during ITI. Results of ongoing studies are expected to answer unresolved questions about the safety, efficacy, and feasibility of concomitant emicizumab and FVIII in ITI.
- Evidence about the risk of inhibitor recurrence after successful ITI and the need for continued FVIII to maintain immune tolerance post-ITI is limited. The potential role of emicizumab alone or in combination with FVIII post-ITI is to be evaluated in the upcoming PRIORITY (PREventing InhibitOR Recurrence IndefiniteLY) study.

This narrative review, which is based on the proceedings of a symposium held July 2020 during the ISTH 2020 Virtual Congress, examines the management of patients with hemophilia A and inhibitors, with a focus on the role of emicizumab during and after ITI.

## 2. The changing face of ITI in the emicizumab era

Prior to the advent of emicizumab, main questions faced by clinicians about ITI were: When to start? What regimen to use? Which product to use? What criteria to use to declare success or failure? Whether or not to perform ITI in patients with newly-developed high-titer inhibitors was never questioned as it was the accepted therapeutic strategy.

Over the past few years, large clinical trials of emicizumab prophylaxis in patients with and without inhibitors have demonstrated low annualized bleeding rates [8–11], particularly in young children with pristine joints [9]. Given the convenient nature of emicizumab administration, which involves infrequent (weekly to every 4 weeks) subcutaneous injections of small volume doses, together with its effectiveness in preventing bleeds, it is arguable whether inhibitor eradication remains necessary in every or even in any case.

The main argument favoring a continued strategy of inhibitor eradication is that patients receiving emicizumab still require hemostatic treatment to treat bleeds (which do occur albeit not often), to manage traumas, and to cover surgical procedures. Bypassing agents and FVIII have been used for these purposes in patients receiving emicizumab prophylaxis. However, thrombotic complications including venous thromboembolism and thrombotic microangiopathy (TMA) have been reported with concurrent use of emicizumab and activated prothrombin complex concentrate (aPCC) at a dose greater than 100 U/kg for more than 1 day [8]. Although thrombotic/TMA events have not been reported with FVIII or rFVIIa in conjunction with emicizumab, aligning with *in vitro* data [12], inhibitor patients with a poor hemostatic response to rFVIIa require rescue with a PCC putting them at risk of thrombotic/TMA events. Thus,

the safest and most effective approach for emicizumab-treated patients requiring hemostatic augmentation (for surgery, treatment of bleeds) is FVIII replacement therapy, which is possible only in the absence of an inhibitor. Inhibitor patients who are not offered ITI may have lifelong reliance on bypassing agents for hemostatic control which is not ideal given their lower efficacy, convenience and safety, and higher costs relative to FVIII replacement therapy (Table 1).

Inhibitor eradication allows for the resumption of FVIII replacement therapy (current and future products) for short term (e.g. surgery) and long-term prophylaxis, and to manage bleeds. Patients who choose to remain on emicizumab post-inhibitor eradication can still benefit from on-demand FVIII to manage bleeds or cover surgery. Moreover, although a rare event, neutralizing antibodies to emicizumab have been reported [13,14]. Inhibitor eradication means that patients who develop neutralizing antibodies to emicizumab can still be treated prophylactically with FVIII rather than with bypassing agents. A further argument in support of inhibitor eradication is to offer patients the possibility of receiving gene therapy in future. Active inhibitors and a history of previous inhibitors are contraindications at present to receiving FVIII gene therapy, but this may change with time.

Despite widespread acceptance of the continuing role of inhibitor eradication in the era of non-replacement therapy, the optimal eradication strategy has yet to be identified: Should emicizumab be administered concurrently with ITI to prevent bleeds? Will ITI regimens change with the use of emicizumab? Should inhibitor patients undergo multiple attempts at eradication as was frequently done in the past? Previously, ITI regimens using large/frequent FVIII dosing (i.e. high-dose ITI) were associated with lower bleeding rates and quicker time to inhibitor tolerance [4], although the trade-off was higher cost and treatment burden. If emicizumab is able to provide bleed prophylaxis during ITI, will there be greater uptake of lower dose/lower frequency ITI regimens? Will governments/insurance payers support the cost of ITI with concomitant emicizumab? Will any role remain for traditional bypassing agent prophylaxis using rFVIIa or FEIBA? Can patients continue to receive emicizumab after successful ITI? Do patients who continue to receive emicizumab post-inhibitor eradication require regular exposure to FVIII to maintain tolerance? New evidence from well-conducted studies is required to resolve these uncertainties and inform recommendations about ITI and inhibitor management.

**Table 1.** Treatment options for hemophilia A patients with or without an inhibitor who require surgery. Comparison between FVIII and bypassing agents.

Inhibitor-negative patients	Inhibitor-positive patients
FVIII (many products available): SHL-FVIII or EHL-FVIII	rFVIIa (black box warning for thrombosis) or FEIBA (black box warning for thrombosis)
More convenient	Less convenient
Less expensive	More expensive
Safe when combined with emicizumab	Less effective and less safe (FEIBA) when combined with emicizumab

EHL = extended half-life; FEIBA = Factor Eight Inhibitor Bypassing Activity; rFVIIa = recombinant activated factor VII; SHL = short half-life.

In recognizing that clinicians still require guidance in the absence of data-driven consensus recommendations, the Future of Immunotolerance Treatment (FIT) Group was established. The group has proposed new algorithms for performing ITI with and without concomitant emicizumab and formulated key conclusions based on available evidence [15]:

- Inhibitor eradication remains a desirable goal.
- As ITI is the only approach that currently offers the possibility of inhibitor eradication, all patients with inhibitors should be offered at least one attempt.
- Emicizumab alone is an option for patients with inhibitors who, for various reasons, must delay or are unable/unwilling to undergo ITI, or fail ITI.
- Where emicizumab is available, the addition of immunosuppressive therapy to ITI is no longer supported.
- As inhibitor patients are likely to undergo fewer ITI courses in future, the choice of initial course (FVIII source and ITI regimen) is likely to become increasingly more important.
- The ability to use emicizumab concomitantly with FVIII during ITI to prevent bleeds may influence the choice of ITI regimen.

### 3. Concomitant use of emicizumab with FVIII during ITI

Although ITI therapy has been in use since the 1970s [16], a universally accepted regimen has not been identified. As regards source, no particular FVIII product has demonstrated superiority over others for a successful ITI outcome. As regards regimen, the international ITI study found no difference in efficacy between high-dose (FVIII 200 IU/kg/day) and low-dose (FVIII 50 IU/kg 3 times/week) ITI regimens in patients with good predictors of ITI success; however, the longer time to tolerance and higher number of bleeds with the low-dose regimen led to early study termination [6]. The bleed protection likely to be provided by concomitant use of emicizumab with FVIII in ITI may obviate the need for high-dose ITI regimens.

At present, published data about the use of emicizumab during ITI are limited. An ITI regimen with concomitant emicizumab in pediatric inhibitor patients, commonly referred to as the Atlanta protocol, has been described [17]. This retrospective chart review study at a single center in Atlanta, Georgia, reported on seven patients (aged 21 months to 12 years) with inhibitors, five of whom had undergone previous ITI attempts. Patients received loading doses of emicizumab (3 mg/kg/week for 4 weeks) followed by standard or extended half-life recombinant FVIII (rFVIII) at a dose of 100 IU/kg 3 times/week (six patients) or plasma-derived FVIII (pdFVIII) at a dose of 50 IU/kg 3 times/week (one patient), concomitantly with emicizumab prophylaxis (1.5 mg/kg/week or 3 mg/kg every 2 weeks). Three patients achieved a negative inhibitor titer, of whom two had normal FVIII recovery  $\geq 66\%$ . No side effects or adverse reactions were reported during a median 35 weeks' follow-up.

Although the results are interesting, the small sample size and ITI status of patients in this retrospective study underlie the need for larger prospective studies to evaluate the safety, efficacy, and feasibility of ITI in combination with emicizumab in ITI-refractory and ITI-naïve patients.

Several studies are either underway or soon to commence to explore the use of emicizumab during ITI. A two-part open-label trial in the United States (US) is planning to examine the safety and efficacy of concomitant use of prophylactic emicizumab with low-dose rFVIII (ClinicalTrials.gov identifier: NCT04030052) [18]. Part 1 will evaluate the incidence of inhibitor development in PUPs and minimally treated patients <3 years of age treated with combination therapy. rFVIII doses will be  $25 \pm 5$  IU/kg at a frequency of every 1–2 weeks. Part 2 will focus on children and young adults <21 years of age with moderate/severe ( $\leq 2\%$  FVIII) hemophilia A and inhibitors receiving the combination of emicizumab and low-dose rFVIII ITI.

Another US-based randomized trial (Inhibitor Eradication Trial; ClinicalTrials.gov identifier: NCT04303572) is comparing rFVIII Fc-fusion protein (rFVIII-Fc) ITI (100 IU/kg daily) plus emicizumab (1.5 mg/kg once weekly after a 4-week induction) vs rFVIII-Fc (100 IU/kg daily) ITI alone. The primary endpoint is inhibitor eradication by week 48 [19,20]. This trial plans to enroll 90 patients with severe hemophilia A and high-responding inhibitors (anti-VIII >5 BU), including patients who develop inhibitors during a companion randomized Inhibitor Prevention Trial; the latter is randomizing 66 PUPs with severe hemophilia A to receive rFVIII-Fc (65 IU/kg once weekly prophylaxis) or emicizumab alone (1.5 mg/kg once weekly after a 4-week induction) (ClinicalTrials.gov identifier: NCT04303559) [21].

A 5-year multicenter, observational retrospective-prospective study referred to as MOTIVATE is underway at centers in the US and Europe (ClinicalTrials.gov identifier: NCT04023019) [22]. MOTIVATE aims to capture the effectiveness and safety of three different approaches for managing patients with hemophilia A and inhibitors: 1) ITI without emicizumab; 2) ITI in combination with emicizumab; 3) emicizumab alone with no attempt at ITI. Primary endpoints are ITI success and bleeding rates. Recruitment began in March 2020 and estimated enrollment is 120 participants.

Lastly, a European prospective, multicenter clinical trial is aiming to examine the safety of the association between ITI and emicizumab prophylaxis in patients (>3 kg and <65 years of age) with hemophilia A and inhibitors. ITI will begin at enrollment in patients already receiving emicizumab or after a loading dose of emicizumab (3 mg/kg/week for 4 weeks) in patients new to treatment. Patients are to receive primary or rescue ITI with rFVIII or pdFVIII at an initial dose of  $50 \text{ IU/kg} \pm 5 \text{ IU/kg}$  3 times weekly plus emicizumab prophylaxis at any approved maintenance dose. To monitor outcomes after successful ITI, tolerized patients will be followed for a further 12 months during which time they will receive one of emicizumab alone, emicizumab with FVIII, or FVIII alone according to the

decision of the investigator and patient/caregiver. Trial registration is pending.

#### 4. Concomitant use of emicizumab with FVIII after ITI

Possible outcomes of ITI are no tolerization, partial tolerization and successful tolerization [23]. For patients who fail ITI, emicizumab to prevent bleeding should be considered standard of care in countries where it is available for use. Treatment with bypassing agents either on-demand or prophylactically can be considered if emicizumab is not available. For patients who are partially tolerized, FVIII concentrates at higher than usual doses can be used to prevent bleeding or, where available, emicizumab can be prescribed. The clinical scenario that, paradoxically, leads to the most uncertainty is how to proceed when ITI is successful. Prior to emicizumab, tolerized patients would resume FVIII therapy but with a different purpose: bleed prevention (prophylaxis) rather than inhibitor eradication which could involve deescalating to a less intense regimen. However, with licensure of emicizumab, successfully tolerized patients now have the option of using FVIII concentrates prophylactically or emicizumab although both approaches have limitations. Continuing FVIII indefinitely requires IV infusions on average 2–3 times per week with current FVIII concentrates, possibly once a week with future FVIII concentrates. The high treatment burden in terms of the time, effort, and pain involved in infusing factor concentrates often results in poor adherence. Switching to emicizumab following successful ITI may reduce treatment burden and improve adherence, but can be considerably more expensive than resuming FVIII. An unresolved issue with emicizumab use is the potential for inhibitor recurrence if tolerized patients have no further regular exposure to FVIII [23].

Little is known at present about the risk of inhibitor recurrence after successful ITI. One multicenter retrospective case series reported on 64 inhibitor patients (median age of 1.6 years at inhibitor onset and median age of 3.3 years at ITI initiation) with severe/moderate hemophilia (FVIII < 2%) who were successfully tolerized between 1998 and 2010 [24]. Among 58 patients assessed for adherence to post-ITI FVIII prophylaxis, a recurrent FVIII inhibitor was detected in 29.3% (12/41) of adherent patients (12/41) and in 29.4% (5/17) of non-adherent patients, suggesting that continued exposure to FVIII after successful ITI may not be necessary to maintain immune tolerance.

To clarify whether ongoing FVIII therapy is necessary to prevent inhibitor recurrence, the investigator-initiated PRIORITY (Preventing InhibitOR Recurrence IndefiniTeLY) study has been designed. This prospective, multicenter, clinical trial plans to randomize inhibitor patients who achieve successful ITI to emicizumab alone or emicizumab plus weekly FVIII. Main inclusion criteria are male patients aged ≤12 years with severe/moderate (FVIII ≤ 2%) hemophilia A and a history of a high-titer inhibitor (>5 BU/mL) who were successfully tolerized within the previous year using any FVIII concentrate according to international consensus recommendations for ITI [25]. The primary outcome is the inhibitor recurrence rate at

96 weeks. Laboratory testing includes FVIII genotyping, measurement of FVIII inhibitor titers, and pharmacokinetic studies to assess FVIII half-life and FVIII recovery. Analyses are planned for results at 24 (interim), 48, and 96 weeks.

#### 5. Conclusion

Even in the current era of non-factor replacement therapy, the hemophilia community continues to favor attempting inhibitor eradication in patients with hemophilia A and high-titer inhibitors in order to preserve treatment options including the resumption of FVIII use. Emicizumab monotherapy is an option for inhibitor patients who must delay or are unable/unwilling to undergo ITI and those who fail ITI.

Emerging evidence suggests that concomitant emicizumab for bleed prevention during ITI is effective and safe and, ultimately, may increase access to ITI by facilitating the adoption of low-frequency regimens (e.g. 3 times/week). Ongoing studies are aiming to resolve remaining uncertainties about the safety, efficacy, and feasibility of ITI in combination with emicizumab during ITI. The role of FVIII to maintain immune tolerance after successful ITI also remains unclear, as evidence about the risk of inhibitor recurrence is limited. The upcoming PRIORITY study aims to determine whether administering emicizumab alone after ITI may be associated with an increased risk of inhibitor recurrence compared to ongoing FVIII exposure (with or without emicizumab).

Evidence accruing from studies of concomitant emicizumab and FVIII during and after ITI is expected to shape future recommendations for managing patients with hemophilia A and inhibitors.

#### 6. Expert opinion

Hemophilia treaters have always feared the development of high-titer inhibitors to FVIII since bypassing agent prophylaxis is less effective, less convenient, and more expensive than FVIII prophylaxis in patients without inhibitors. Consequently, clinicians would always promote one or more attempts at ITI to hopefully eradicate the inhibitor and return the patient to a non-inhibitor state.

The situation changed with the licensing of emicizumab which has proved to be highly effective at preventing bleeds (much more so than traditional bypassing agents) in patients with inhibitors. However, emicizumab is not a complete solution. Emicizumab is expensive, does not prevent all bleeds, and is insufficient on its own to prevent bleeding in the setting of surgery/major trauma. Concomitant use of emicizumab and aPCC is associated with increased thrombotic risk, and there is a remote possibility that patients may develop neutralizing antibodies to emicizumab. As such, clinicians face several uncertainties: Do we continue to promote ITI in an attempt to eradicate inhibitors? Do we incorporate emicizumab into ITI regimens? Do we continue emicizumab post-inhibitor eradication and, if so, with or without FVIII? If FVIII is continued, at what dose, what frequency, and for how long?

With new developments in hemophilia A still on the horizon, including much longer acting rFVIII concentrates and gene therapy, our view is that inhibitor patients should undergo at least one attempt at ITI to improve their immediate and long-term health status and to maintain options for future treatment. The introduction of emicizumab to the therapeutic arsenal for hemophilia A has led to much improved outcomes in those with high-titer inhibitors but has also generated many questions about the optimal management of patients with inhibitors.

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