POINT-COUNTERPOINT

blood advances

POINT Implementing emicizumab in hemophilia inhibitor management: emicizumab should be prescribed after tolerance

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This article has a companion Counterpoint by Le Quellec and Negrier.

Hemophilia is an X-linked bleeding disorder characterized by deficiency of factor VIII (FVIII), known as hemophilia A, or FIX, known as hemophilia B, which left untreated results in early death and permanent disability. Currently, patients receiving clotting factor replacement concentrates (CFCs) can expect to have healthy joints and a normal life expectancy.[1] Unfortunately, a common complication of CFCs is the development of neutralizing antibodies (inhibitors), which render factor therapy ineffective. For inhibitor patients, bleeding can be treated either episodically or prophylactically with bypassing agents (activated prothrombin complex concentrates [APCC; FEIBA, Shire, Dublin, Ireland] or recombinant activated factor VII [rFVIIa; Novoseven, Novo Nordisk, Bagsvaerd, Denmark]); however, these agents are not as effective as replacing the missing factor with CFCs.[2] As such, patients with inhibitors have both worse morbidity[3,4] and mortality.[5] Thus, the major goal for such patients is eradicating the inhibitor. The only known effective approach to achieve this involves repeated injections of CFCs, a treatment modality called immune tolerance induction (ITI). Considering the subject of this debate, the remainder of the discussion will be restricted to inhibitors in hemophilia A. More specifically, this therapy involves daily or every-other-day injection of CFC, and as ITI is usually conducted in young children, a central venous catheter (CVC) is often required, and the treatment burden and costs are very high. Finally, this approach is effective in ~70% of cases but is lower (~40%) in an intention-to-treat analysis demonstrating the difficulty of adhering to ITI.[6] Although achieving a higher success rate is an important goal for the future, ITI, nevertheless, remains the most effective way to eradicate inhibitors.

Recently, a novel bispecific antibody (emicizumab-kxwh, Hemlibra; Roche, Basel, Switzerland) was licensed in the United States and Europe for the prevention of bleeding in hemophilia A patients with inhibitors. This agent has demonstrated remarkable reductions in bleeding episodes in adolescents/adults in the HAVEN 1 study[7] and even more dramatic results in the ongoing pediatric HAVEN 2 study.[8] Prior to the availability of this drug, a debate such as this would not even be considered, and it is quite remarkable that the mere idea of not recommending ITI to all patients is even being discussed and a testament to the efficacy demonstrated in the emicizumab clinical trials.

With this in mind, there are several arguments, however, in favor of continuing to recommend ITI (Table 1). First, the mortality of inhibitor patients remains higher than those without inhibitors and is directly attributed to bleeding events.[5] Second, treatment of breakthrough bleeding episodes in patients with emicizumab has resulted in serious adverse events, problems not encountered in noninhibitor patients treated with CFCs. Third, patients with inhibitors are not eligible for gene therapy trials, and when commercialized, the presence of an inhibitor may disqualify a patient from a potentially curative therapy. Finally, with such a novel therapy as emicizumab, there remains uncertainty regarding the long-term outcomes of patients who would be left with lifelong (no ITI) inhibitors.

With respect to mortality, a number of studies have evaluated this important issue in inhibitor patients with mixed results[9-12]; however, the largest and most recent study was conducted in the United States utilizing the Centers for Disease Control Surveillance system.[5] More than 7000 males with hemophilia were included in this retrospective analysis including 432 deaths. Importantly, patients who were tolerized were not considered as inhibitor patients in this study. In the multivariate analysis, inhibitor patients had a 70% higher likelihood of dying, and bleeding as a cause of death was more than threefold higher than for noninhibitor patients. Perhaps this alone is sufficient evidence to warrant that every new inhibitor patient undergo ITI.

As described, emicizumab has demonstrated remarkable efficacy at preventing bleeding in inhibitor patients with reductions of 87% and 79% compared with episodic and prophylactic bypassing agent therapy, respectively.[7] Perhaps even more relevant is the 99% reduction in bleeding seen in HAVEN 2 as

Table 1. Pros and cons of ITI vs emicizumab without ITI

	Pros	Cons
Mortality	Patients with inhibitors have increased mortality.	Data regarding mortality predate the licensure of emicizumab and may not apply with emicizumab available.
Breakthrough bleeding treatment	Treatment of breakthrough bleeding is much simpler, safer, and less costly with factor replacement than with bypassing agents.	Breakthrough bleeding is infrequent with emicizumab. Mitigation strategies have demonstrated the ability to treat breakthrough bleeds safely.
Unforeseen adverse events	Emicizumab is a novel agent, and only ~400 patients have ever received it. It is always possible that unforeseen adverse events could occur. Treatment with factor replacement is known to be very safe (with the exception of inhibitor formation).	The mechanism of action of substituting for FVIIIa suggests nonthrombotic-type events should not occur or be rare. Monoclonal antibodies have been in widespread use for several decades, and unforeseen side effects are uncommon.
Gene therapy	Gene therapy when it becomes available may not be effective in patients with active inhibitors but could be effective in patients who have been tolerized.	Some animal data suggest that gene therapy could lead to tolerization when active inhibitors are present.

this pediatric study more closely reflects the patient population that would undergo ITI.[8] Nevertheless, breakthrough bleeding, surgical procedures, and episodes of trauma will occur necessitating treatment with bypassing agents, and when bypassing agents (particularly APCC) were administered to patients on the HAVEN 1 trial, serious thrombotic events occurred in 2 subjects, and thrombotic microangiopathy (TMA) occurred in 3 subjects approximating 5% of the study population. It should be noted that these events occurred when APCC was used at relatively high doses (>100 IU/kg per day) for >24 hours. There have been no known occurrences of TMA when treating noninhibitor (or tolerized) patients for bleeding with CFCs. Furthermore, although thrombosis has occurred in hemophilia patients, it is exceedingly rare and generally provoked by CVCs or surgical procedures. In essence, treatment with CFCs in noninhibitor patients is extremely safe, whereas treatment of bleeding in inhibitor patients either with bypassing agents or, in particular, with bypassing agents concomitantly with emicizumab carries with it a thrombotic risk. Accordingly, it should be noted that APCC and rFVIIa both carry black box warnings for the risk of thrombosis, and emicizumab has a black box warning regarding thrombosis and TMA when it is combined with APCC. As such, avoiding bypassing agents (with or without emicizumab) is an important goal in the management of inhibitor patients, and this can only be accomplished if ITI is performed successfully.

The next reason to pursue ITI is perhaps more theoretical currently but involves the potential for a future phenotypic cure of hemophilia. Recently, noteworthy results from early clinical trials for a FVIII gene therapy approach were reported whereby 13 subjects treated with the 2 highest doses achieved sustained normal factor levels; that is, they were cured of hemophilia.[13] This trial excluded patients both with current and a history of inhibitors. Assuming this therapy becomes commercially available (possibly in the next 5 years), adult patients with hemophilia A without inhibitors could opt for this curative approach. Although animal studies have suggested that gene therapy could lead to immune tolerance in dogs with inhibitors,[14] the prospect that this will occur in humans is entirely unclear. Until such data are demonstrated in humans (and this will take years to generate), the safest assumption is that gene therapy will not be made available to patients with active inhibitors. Thus, pursuing ITI for all inhibitor patients should remain the goal so as not to end up with a cohort of young men who could be ineligible to be cured of hemophilia.

Finally, we are left with what could be called "unknown unknowns," that is, the uncertainty that emicizumab may result in unexpected and unintended harmful consequences. Taking the extensive preclinical data, the mechanism of action, and the fact that >200 inhibitor patients have been treated (some for >2 years), it is entirely possible, if not likely, that emicizumab will not lead to unexpected untoward effects, but only several years more of data can entirely remove this uncertainty inherent to all new technologies. Thus, until such data are generated, the prospect of abandoning ITI in favor of emicizumab alone should be undertaken with this, albeit, theoretical concern.

For those patients who do undergo ITI and are successful, we are, unfortunately, left with a quandary. In the current situation, all patients who are tolerized continue on FVIII therapy in the form of prophylaxis with the express goal of bleed prevention; however, this ongoing exposure to FVIII is also achieving the goal of maintaining tolerance. Little to nothing is known about the consequences of achieving tolerance and then purposefully abandoning FVIII prophylaxis. In other words, once tolerance is achieved, is it lifelong, or will inhibitors recur in the absence of continued exposure to FVIII? At this time and given the available information, one cannot recommend to simply use emicizumab alone in tolerized patients, meaning that patients will still need to continue FVIII therapy. The research questions that must be addressed in order to inform decision making in the future include an understanding of first whether continued, regular exposure to FVIII is necessary, and if so, what is the least burdensome way this can be achieved? How infrequent could it be done? Can a subcutaneous approach be used solely for the maintenance of tolerance?

Although I have argued in favor of continuing to pursue ITI in new inhibitor patients rather than treating them exclusively with emicizumab, it should be pointed out that these 2 approaches are not mutually exclusive. Although patients on ITI were excluded from HAVEN 1 and HAVEN 2, the labeled indication does not exclude concomitant treatment with ITI and emicizumab. Importantly, such therapy should be safe given the mechanism of action of emicizumab and CFCs.[15] In fact, considering the high risk for bleeding during ITI as has been demonstrated[6] and the joint damage that such bleeds can result in, an entirely new approach to ITI makes perfect sense. The International ITI study demonstrated equal efficacy for the success of ITI between a high-dose daily regimen and a low-dose every-other-day regimen.[6] The study was discontinued early because of a higher bleeding rate in the

low-dose arm; however, the low-dose arm is less burdensome and far less expensive as it utilizes only 12.5% of the factor needed in the high-dose regimen. Furthermore, the low-dose regimen could potentially avoid the use of CVCs. Thus, low-dose ITI coupled with emicizumab could result in successful tolerization while preventing bleeding and preserving joint function. Based on the cost of ITI in the United States, this combined approach would be less expensive than the high-dose ITI approach. Alternatively, emicizumab alone could ultimately reduce the cost of care for inhibitor patients in general including those for whom ITI is not performed because the overall costs of ITI while not formally studied in comparison with emicizumab alone are likely substantially higher.

In summary, inhibitor eradication remains the most important goal of the management of inhibitor patients given the higher mortality, risks associated with treating breakthrough bleeding, and preserving the prospect for gene therapy. Prevention of bleeding during the long course of ITI is also important such that tolerized patients do not emerge from ITI with permanently damaged joints. Emicizumab has shown a remarkable ability to prevent bleeding particularly in the younger age group, the same age group that presents with inhibitors. Thus, moving forward, novel approaches to achieve tolerance, perhaps with even lower doses or alternative administration routes, in combination with emicizumab to prevent bleeding should be a goal for future research.

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