EDITORIALS

# Mimicking Factor VIII to Manage the Factor VIII–Deficient State

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Hemophilia A is an X-linked disorder caused by defective factor VIII, which until now has involved factor VIII replacement to treat and prevent bleeding in joints, muscles, and other body cavities. Although factor VIII replacement is effective, the treatment burden is high, because intravenous access occurs several times weekly and the therapy is complicated by inhibitor antibody development in up to 30% of patients. Thus, interest is intense in new therapeutic agents for the restoration of hemostasis in patients with hemophilia. One such agent is the factor VIII mimic emicizumab (Hemlibra), which was investigated in a trial by Mahlangu et al.,[1] the results of which are reported in this issue of the *Journal*.

So, how did the concept of a factor VIII mimic arise? In 2012, Kitazawa and colleagues[2] recognized the therapeutic potential of a bispecific IgG antibody that binds factor IXa and factor X with a spatial proximity that is similar to the proximity used by the cofactor function of factor VIIIa (Fig. 1). By binding and bridging factors IXa and X, the bispecific antibody emicizumab mimics the interaction of factor VIII with factors IXa and X (one of the factor VIII cofactor functions), thus promoting hemostasis. In preclinical studies, the bispecific antibody increased in vitro factor Xa generation, shortened the activated partial thromboplastin time, and shortened the thrombin time in factor VIII–deficient plasma and reduced blood loss after muscle injury in a cynomolgus monkey model of hemophilia.[3,4] In clinical trials, including a phase 1–2 trial involving 18 patients who had hemophilia A with or without inhibitors and a phase 3 trial involving 109 patients who had hemophilia A with inhibitors, the annualized bleeding rate was approximately 90% lower with emicizumab prophylaxis, administered subcutaneously, than with no emicizumab prophylaxis.[5,6] In November 2017, the Food and Drug Administration approved emicizumab for the prevention of bleeding events in patients with factor VIII inhibitors.

Mahlangu et al. report the results of a phase 3 trial involving 152 patients who had hemophilia A without inhibitors. The investigators found that emicizumab, administered subcutaneously weekly or every other week, prevented bleeding events and was superior to historical factor VIII treatment. The annualized bleeding rate was at least 94% lower with emicizumab than with placebo among patients who had received factor VIII on demand previously (to treat bleeding events), and the rate was 68% lower with emicizumab than with previous prophylaxis among patients who had received factor VIII prophylaxis (to prevent bleeding events). Breakthrough bleeding events were treated with factor VIII concentrate, and the investigators did not observe any thrombosis or thrombotic microangiopathy — events that had occurred in a previous trial of emicizumab in patients with inhibitors in which prothrombin complex concentrate was administered for breakthrough bleeding events.[6] The absence of thrombosis with factor VIII concentrate is probably related to the fact that factor VIII has an affinity for binding factors IXa and X that is 10 times as high as that of emicizumab,[7] so it displaces emicizumab, thereby avoiding potential additive toxicity.

A survey that was conducted in this trial indicated that emicizumab was preferred over fac-

tor VIII, but there was no direct comparison, nor was the basis specified for the preference, such as a simpler route of administration or a reduction in the incidence of joint bleeding events or pain severity. Blood in a joint over time leads to cartilage damage with synovial inflammation, production of cytokines (e.g., interleukin-1$\beta$ and interleukin-6), immune activation, and joint degeneration.[8] Is joint aching, pain, or persistent bleeding or effusion after breakthrough bleeding events similar in frequency or severity in patients receiving emicizumab and those receiving factor VIII prophylaxis? Although both drugs bind factor IXa and factor X to promote hemostasis, biochemical differences exist between these proteins that may affect clinical hemostasis.[7] For example, factor VIII also promotes phospholipid binding and stabilizes the factor IXa active site, and it interacts at multiple sites with factor IXa and factor X, as compared with the single-site binding by emicizumab. Factor VIII has an on–off mechanism, unlike emicizumab, as well as a greater degree of self-regulation than emicizumab. Whether these differences predict clinical differences in the severity of joint disease between patients receiving emicizumab therapy and those receiving factor VIII remains unknown. Prospective monitoring of joint pain, range of motion, and ultrasonographic findings may help to assess this question.

Another consequence of blood-induced immune activation may be inhibitor formation. It is of interest that one trial participant who had an inhibitor in the past and had undergone induction of immune tolerance was observed to have recurrent detection of low-titer anti–factor VIII antibody, a finding that suggests incomplete inhibitor suppression by emicizumab prophylaxis. Although the inhibitor titer decreased, it persisted despite continued therapy. The determination of whether this situation differs from inhibitor suppression in patients who have undergone induction of immune tolerance with factor VIII prophylaxis will involve future prospective study. Does emicizumab prophylaxis promote factor VIII tolerance in previously untreated patients? If emicizumab prophylaxis allows children to avoid factor VIII exposure in early life and during severe bleeding events in which intense factor VIII exposure occurs (both of which are major risk factors for inhibitor formation), will inhibitors be prevented or delayed?

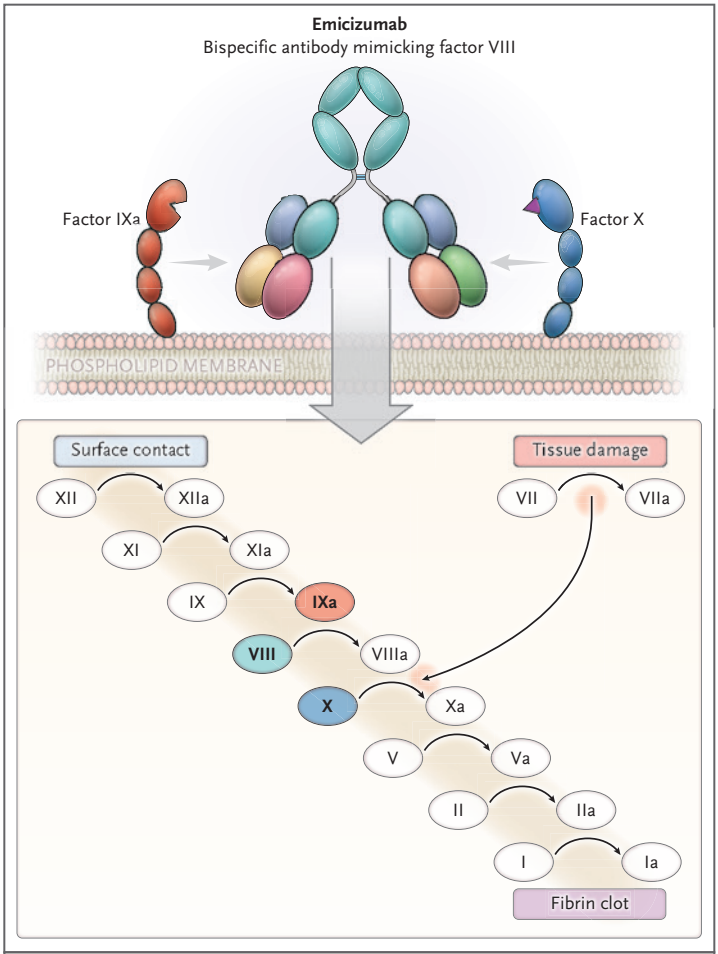


**Figure 1. Emicizumab Binding to Factor IXa and Factor X.**
Emicizumab mimics factor VIII by binding to factor IXa and factor X to generate factor Xa, which substitutes for the missing factor VIII to promote hemostasis in persons with hemophilia A.

Finally, how might emicizumab therapy be implemented in the management of hemophilia? Will emicizumab be effective in treating acute bleeding? What is the role of age, severity, or degree of joint damage in the decision to switch to emicizumab therapy? What cost will society accept for a drug that reduces disease burden? Although emicizumab therapy is cost-effective in patients with a hemophilia inhibitor,[9] is emicizumab prophylaxis cost-effective in a patient without an inhibitor who has a better response to treatment, higher quality of life, and fewer hospitalizations? Until more is known, it will be important for discussions between providers and patients to focus on risk, benefit, cost, and par-

ticipation in observational studies and clinical trials.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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# Of MICs and Men

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In medicine, we often collect data that lie on a quantitative spectrum. However, dealing with shades of gray is always complex. To simplify decision making, we reduce values to binary descriptors, such as above or below normal or within or outside a certain quartile. This is true in the clinical microbiology laboratory that reports out the results of antibiotic testing as "susceptible" or "resistant." But, as Colangeli et al.[1] report in this issue of the *Journal*, simplification can be quite misleading, especially when it comes to the treatment of tuberculosis.

As with other infectious diseases, therapy for tuberculosis is guided by in vitro susceptibility testing. Bacteria that are isolated from patients can be assayed by a variety of methods and classified according to their susceptibility to a panel of drugs. In the case of tuberculosis drugs, this information is used in a binary way to determine whether a patient is likely to have a response to standard therapy or, if antibiotic resistance is present, whether treatment requires a more tailored approach.

How well does this classification system work? Most often, standard four-drug treatment is successful, with cure rates of more than 90% reported in several clinical trials. Still, such therapy fails to clear the infection in a substantial number of patients or results in a relapse of active disease. Such results have variously been attributed to poor drug adherence or to variations in the characteristics of the infected patients or the infecting pathogens.

To determine whether bacterial factors play an important role in treatment failure, Colangeli et al. took advantage of the fact that samples had been stored for a group of patients who were enrolled in the Tuberculosis Trials Consortium Study 22,[2] in which two different treatment regimens were compared. Although the study was completed in 2001, isolates of the causative organisms were available for most patients who had a relapse after therapy, both from before the start of treatment and after relapse occurred. The investigators hypothesized that bacterial isolates from patients who had a relapse would be less susceptible to antibiotics, although not to the extent that they would be labeled as having antibiotic resistance.

Using isolates from patients who had a relapse and those who were successfully cured, the researchers determined the lowest concentrations of both isoniazid and rifampin that would inhibit growth — the minimal inhibitory concentration (MIC). They used a method that could