Comment on Callaghan et al, page 2231

In hemophilia, it just keeps getting better

Aric Parnes | Brigham and Women's Hospital

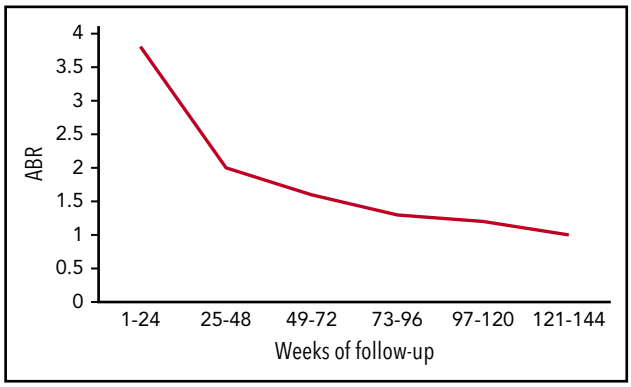
Long-term follow-up for novel therapies is essential to confirm initial safety and efficacy data, but how often does that long-term follow-up show better results than the initial studies? In this issue of *Blood*, a 2-year follow-up to the HAVEN trials by Callaghan et al[1] studying emicizumab for prophylaxis in severe hemophilia A with and without inhibitors has done just that.

Emicizumab is a bispecific antibody that binds factors IXa and X to mimic the function of factor VIII. Its appeal comes down to 3 large breakthroughs that each on its own might have shifted patient choice. First, emicizumab is not recognized by inhibitors of factor VIII because it is NOT factor VIII. This allows it to function in patients with and without inhibitors, a clear victory for inhibitor patients who have previously had inferior therapeutic options. Second, emicizumab is administered subcutaneously, a major improvement compared with the IV route of traditional factor concentrates. Third, the half-life of 30 days is an enormous leap from 12 to 24 hours of factor VIII concentrates, including extended half-life products. However, these characteristics say little about its efficacy and safety.

The HAVEN 1 to 4 trials[2-5] divided patients into randomized arms by age (<12 and 12+), inhibitor status, and dosing schedule (weekly, every other week, or every 4 weeks). Compared with the patients using factor VIII or bypass agents for prophylaxis, annualized bleeding rates (ABRs) improved with emicizumab by 79%, 99%, and 68% in HAVEN 1 to 3, respectively.

In the current update, Callaghan et al followed the patients from HAVEN 1 to 4 for 2 years and found ABR declining over time. Using pooled data between studies, the mean ABR for all bleeds fell from 3.3 in the first 24-week period to 1.0 in the final-week period (see figure). This improved trend was captured not only in ABR for all bleeds but also in the number of patients reporting zero all bleeds, 0 to 3 all bleeds, 0 to 3 target joint bleeds, and factor VIII consumption. Perhaps most striking is that bleeding rates for inhibitor patients are now on par with those of noninhibitor patients.

Activated prothrombin complex concentrate (aPCC) consumption also declined over time, not surprisingly since the announcement that its use with emicizumab should be avoided because of thrombotic risk. This led to a diversion of aPCC to recombinant activated factor VII (rFVIIa) for treatment of acute bleeds in inhibitor patients and may explain the slight increase in rFVIIa usage during treatment midstudy intervals (weeks 49 to 120). This diversion makes the overall decline in rFVIIa consumption more notable.



Mean ABR of all bleeds over time. The figure has been adapted from data in Table 2 in the article by Callaghan et al that begins on page 2231.

Why bleeding rates and target joints might improve over time warrants more exploration. Perhaps, a decrease in bleeding events leads to increased activity, exercise, and bone and joint health, whereas improved joint health, coming full cycle, results in further declines in bleeding. In addition, improved hemostasis may prevent recurring microbleeding and chronic inflammation in the joint space. Could these improvements in joint health eventually reset the threshold for initiation of acute hemarthrosis?

In the initial HAVEN 1 trial,[2] 5 inhibitor patients developed thrombotic complications, including 3 with thrombotic microangiopathy (TMA) when acute bleeds were treated with aPCC at higher cumulative doses (>100 U/kg/24 hours) for extended periods of time (≥24 hours). The TMAs resolved once aPCC was stopped. Most reassuring in the 2-year follow-up is that no additional thromboses or TMAs occurred after restriction of aPCC was instituted. Also, no new safety concerns appeared. However, in all the HAVEN studies, only 26 patients were age 65 or older. One of these patients suffered a myocardial infarction and was found to have coronary artery disease. Future data for patients with cardiac risk factors on emicizumab will be welcome.

What is the frequency of anti–emicizumab antibody development? In the initial HAVEN publications,[2-5] the rate was 1.0% of patients (4/398), although only 2 (0.5%) of these antibodies were neutralizing, compromising the efficacy of emicizumab. With enhanced testing, 14 (3.5%) anti–drug antibodies were found, only 3 with neutralizing potential (0.8%), including 1 patient who switched back to factor VIII infusions for prophylaxis.[6] Whether the enhanced test or the additional drug exposure time led to increased detection of anti-drug antibodies is unclear. The authors are planning to report a separate update regarding emicizumab's immunogenicity. Still, these numbers seem like an improvement compared with traditional factor VIII concentrates, which stimulate anti–factor VIII inhibitor development in

up to one-third of severe hemophilia A patients.

Altogether, it becomes clear why patients report improvements in quality of life and a strong preference to remain on emicizumab.[7] For patients and providers cautious about accepting new advances, the work by Callaghan et al comes as a welcome addition to the previous landmark HAVEN trials. With 2 years of follow-up confirming its safety and efficacy, emicizumab should be considered the standard of care for severe hemophilia A prophylaxis in patients with and without inhibitors. With these exciting data on emicizumab and prospects for other nonfactor therapies around the corner, hemophilia care just keeps getting better.

Conflict-of-interest disclosure: The author receives research funding from and serves on the advisory board for Genentech. ■

REFERENCES

1. Callaghan MU, Negrier C, Paz-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1-4 studies. *Blood*. 2021;137(16):2231-2242.
2. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809-818.9.
3. Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood*. 2019;134(24):2127-2138.
4. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379(9):811-822.
5. Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. *Lancet Haematol*. 2019;6(6):e295-e305.
6. Paz-Priel I, Chang T, Asikanius E, et al. Immunogenicity of emicizumab in people with hemophilia A (PwHA): results from the HAVEN 1-4 studies [abstract]. *Blood*. 2018;132(suppl 1). Abstract 633.
7. Kempton C, Trask P, Parnes A, et al. Development and testing of the Satisfaction Questionnaire with intravenous or subcutaneous hemophilia injection and results from the phase 3 HAVEN 3 study of emicizumab prophylaxis in persons with haemophilia A without FVIII inhibitors. *Haemophilia*. In press.

DOI 10.1182/blood.2020010238

TRANSPLANTATION

Comment on Song et al, page 2243

Using the binary language of IL-2 to prevent GVHD

Everett H. Meyer | Stanford Medical School

In this issue of *Blood*, Song et al[1] identified a new means of selective blockade of the interleukin 2 (IL-2) pathway during hematopoietic cell transplantation that prevents graft-versus-host disease (GVHD) and augments donor graft-versus-leukemia (GVL) immunity. Using preclinical murine major histocompatibility complex mismatch models of hematopoietic stem cell transplantation, the group used a monoclonal antibody, JES6-1, that binds to IL-2 and selectively interferes with IL-2 binding to specific subunits of the IL-2 receptor (ie, the IL-2 receptor β and γ subunits but not the IL-2 α subunit). This study is among a number of exciting recent developments in our understanding of IL-2 biology and the potential implementation of whole new classes of clinical interventions targeting IL-2.

The importance of the IL-2 pathway in transplantation is underscored by the pivotal role that calcineurin inhibitors played in advancing transplantation. Calcineurin inhibitors act in large part by blunting T-cell receptor signaling and reducing the ability of immune cells to produce IL-2. This includes $CD4^+$ helper T cells, which are a major source of IL-2 that drives both their own autocrine expansion and that of other cells such as effector CD8 T cells. Calcineurin inhibitors such as tacrolimus have known toxicities, but they remain the backbone of most strategies to prevent GVHD.[2] As Song et al again demonstrate in their study, calcineurin inhibitors can impede the GVL effects of donor T cells.

IL-2 has been shown to be plieotropic and can sometimes exert apparently contradictory effects.[3] This is in part because IL-2 binds to dimeric receptors of 2 general types: the IL-2RαIL2Rγ receptor, which is expressed on activated T cells and regulatory T cells (Tregs), and the IL2RβIL-2Rγ receptor, which is expressed on immunologically active T, B, and natural killer (NK) cells. Administration of IL-2 at certain doses can, for example, cause Tregs to expand. This has been used as a clinical strategy to treat chronic GVHD,[4] but at other doses, IL-2 can worsen alloimmune responses and drive T cell or NK reactivity. Monoclonal antibodies that block certain IL-2 receptors or designer IL-2 mutant proteins that bind to the IL-2RαIL-2γ receptors preferentially have been shown to increase Treg numbers and are being evaluated in clinical trials to induce immune tolerance.[5]

Song et al used the antibody JES6-1 to selectively block IL-2 from binding to IL-2 receptors made from the β and common γ chains but not receptors made from the α and common γ chain I (CD25) that Tregs depend on. This reduced donor T-cell proliferation reduced the number of $CD4^+$ T cells in the colon and liver, which are GVHD target organs. Inflammatory cytokines such as granulocyte colony-stimulating factor are also reduced. As experimental controls, they used a rat immunoglobulin G (IgG) isotype antibody, and the anti–IL-2 S4B6 antibody that binds to IL-2 allows for some engagement of IL-2 receptors that use the β chain and common γ chain. Compared with control antibodies, Song et al show that JES6-1–treated mice have significantly less severe GVHD and better survival.

In an extensive mechanistic evaluation, the group showed that multiple interrelated pathways are altered to prevent GVHD using this selective antibody approach. Based on other studies, one would first suspect that conventional $CD4^+CD25^+FOXP3^+$ Tregs are primarily responsible for GVHD protection because increasing Treg numbers in other