3 years is unknown, as is the effect of long-term treatment with these agents.

The authors recommend that all high-risk patients be considered for treatment with BCRi/BCL2a, preferably in a clinical trial. HSCT should be considered for patients who fail to respond, as well as for certain responders. Younger patients with no comorbidities, a good donor, and high-risk disease are still appropriate candidates for HSCT, whereas older patients with significant comorbidities, poor donor options, and lower risk disease may be more appropriately continued on the novel agent. The question of which is a superior strategy is unlikely to be answered definitively without a prospective study, and the premature closure of Alliance 100701 indicates that a transplant study in CLL may be difficult to complete. However, HSCT and BCRi may have complementary roles. Ibrutinib has evidence of efficacy in murine GVHD models,10 and a clinical trial evaluating its effect against steroid-refractory chronic GVHD is ongoing (#NCT02195869). It is interesting to think about how BCRi could be used earlier after HSCT to augment disease control while GVL is being established, particularly if it can attenuate chronic GVHD. As we learn more about the long-term effects of BCRi/BCL2a, we will be able to make more clear recommendations with respect to the role of HSCT, but until more is known, HSCT remains an important treatment modality for patients with high-risk CLL. Along with experts in CLL, HSCT experts should continue to have a role in ensuring patients are fully informed with respect to all of their therapeutic options as we enter a new era in CLL management.

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REFERENCES

Comment on Collins et al, page 3880

GlycoPEGylated factor IX: a new step forward

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In this issue of Blood, Collins et al provide the results of a prospective, randomized, single-blind, phase 3 trial on the use of nonacog beta pegol, a new long-acting glycoPEGylated factor IX (FIX) molecule for the treatment and prevention of bleeding episodes in 74 patients with hemophilia B.1

It was 50 years ago that Dr Judith Pool published a paper about cryoprecipitate, the first form of replacement therapy for patients with hemophilia.2 There have been many steps forward in hemophilia therapy since that seminal discovery. Clotting factor VIII (FVIII) and FIX concentrates were first derived from human plasma, and in the 1990s, they were manufactured using the recombinant technology.3,4 During the last 2 decades, the availability of safe and effective replacement therapy has changed the natural history of the disease, thanks to rapid bleeding control and the widespread use of prophylaxis, which is the standard of care aimed at avoiding crippling joint damage.

In addition to its undeniable benefits, replacement therapy still has drawbacks mainly related to the intravenous route of administration and the relatively short half-life of clotting factors. Recently, bioengineered molecules have been developed to overcome some of these limits. In particular, long-acting FIX molecules, although still delivered intravenously, will have a profound effect on prophylaxis feasibility and adherence to treatment in patients with hemophilia B.
Until now, 3 long-acting FIX molecules have been studied for weekly prophylaxis, but results from phase 3 trials are available only for 2 of them: nonacog beta pegol and rFIXFc.1,5

In the phase 3 trial reported by Collins et al, weekly prophylaxis with 10 and 40 IU/kg and on-demand treatment with nonacog beta pegol were assessed in patients with severe hemophilia B.1

Many aspects of this new long-acting FIX concentrate deserve consideration:

- The terminal half-life of 96 to 110 hours, which is fivefold longer than that of unmodified FIX, allowed the performance of successful prophylaxis with no more than 1 injection per week. This implies at least a 50% reduction in the number of total injections per year, with significant advantages in terms of quality of life, adherence to prescribed treatment, and less need of central venous lines insertions in the pediatric population.
- The in vivo recovery of nonacog beta pegol was twofold higher compared with standard recombinant FIX, resulting in higher plasmatic FIX levels while using lower doses during weekly prophylaxis.1
- As shown in the figure, patients treated with 40 IU/kg/week maintained FIX trough activity well above 25 IU/dL, ensuring good protection from breakthrough bleeds and thus allowing a normal active life. These results support increasing the interval between injections and may allow prophylaxis with 1 injection every 2 to 3 weeks on the basis of individual pharmacokinetics.
- The high efficacy rate by means of a single injection and the successful protection from bleeding into target joints is reassuring. In fact, up to 99% of bleeds were resolved with a single injection, and up to 70% of patients with established target joints at study entry did not bleed in their target joints during the trial.
- A good safety profile was confirmed because no patient developed neutralizing anti-FIX inhibitors.
- Finally, at variance with rFIXFc,5 annualized bleeding rates were twofold lower and the success rate of bleeding control with a single injection was slightly higher with nonacog beta pegol, suggesting that this molecule may convey superior efficacy than rFIXFc, although a head-to-head comparison would be needed to confirm this.

In this light, long-acting FIX molecules represent a terrific advance in hemophilia care, and the results presented in the paper by Collins et al2 confirm this. However, in addition to all the tangible advantages, several aspects still need to be further investigated:

- The long-term safety related to the chronic exposure to the polyethylene glycol moiety;
- The meaning and relevance, if any, of the development of noninhibitory antibodies already reported in the phase 3 trial,1 as well as the immunogenicity of the molecule in previously untreated patients;
- The adequacy and reliability of current clotting factor laboratory assays to predict and monitor treatment efficacy; and
- The cost-effectiveness of the new drug compared with standard products, taking into account the possibility of treatment optimization and individualization.

All in all, with this new molecule, which will hopefully soon be available on the market, the progress of hemophilia replacement therapy has taken an additional step forward to ameliorate treatment feasibility and patients’ quality of life.

**REFERENCES**


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**Comment on Xu et al, page 3978**

**HMGB1 takes a “Toll” in sickle cell disease**

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In this issue of *Blood*, Xu et al elegantly demonstrate that high mobility group box 1 (HMGB1) contributes to the endogenous armamentarium to activate Toll-like receptor 4 (TLR4) in sickle cell disease (SCD).1

SCD is the most common monogenic disease, which occurs due to a single amino acid substitution in the hemoglobin, resulting in the expression of sickle hemoglobin (HbS) and sickle-shaped red blood cells (RBC).2 The homozygous disease is characterized by a complex pathophysiology replete with inflammation, oxidative stress, multiorgan damage, pain, and reduced life span. Enormous phenotypic variability contributes to poor disease management resulting in lifelong suffering and poor quality of life. In addition to hemolytic anemia, intermittent and unpredictable episodes of vasoocclusive crises due to adhesion of sickle RBCs in the vasculature impair oxygen and blood supply to the organs, resulting in cumulative organ damage and acute pain.2 It is believed that ischemia/reperfusion injury (I/R) is a major contributor to the complex disease pathobiology,3 but no common targets are defined to ameliorate the clinical manifestations.

Emerging studies are suggestive of the involvement of TLR4 in organ damage and pain at a multicellular level in SCD. We observed that TLR4 transcripts are increased in the spinal cord of mice expressing human HbS compared with control mice expressing normal human hemoglobin.4 Subsequently, Ghosh et al demonstrated that hemin-induced TLR4 activity leads to acute lung injury.
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