What's ahead in the treatment of hemophilia - Section 3

Modified factor VIII and factor IX recombinant products

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Introduction

The preferred form of replacement therapy for patients with severe hemophilia is long-term regular prophylaxis, which has shown to reduce bleeding frequency particularly into joints, therefore reducing the development of chronic arthropathy and improving patients’ quality of life.1,2 Patients on prophylaxis with standard recombinant factor VIII (FVIII) require intravenous injections every other day or three times per week (hemophilia A), while those with hemophilia B receiving standard factor IX (FIX) are commonly treated twice weekly. These regimens are based on the specific factor half-life that is longer for FIX than for FVIII (18-20 h versus 10-12 h).3,4 New modified FVIII and FIX molecules endowed with extended half-life are in development or have been recently licensed (Table 1). These products have the potential to improve prophylaxis feasibility promoting patient adherence and reducing the burden of frequent intravenous injections or, especially in children, the need for central venous lines.5,6 Another favorable aspect is the possibility to maintain high trough levels during prophylaxis and these may be associated with improved clinical outcomes and more active life-style.5,6 Finally, the use of extended half-life factors in the surgical setting may allow for less frequent dosing regimens and lower factor consumption while maintaining full hemostatic efficacy.5

Current state-of-the-art

A variety of technologies have been used to improve the pharmacokinetic profile of recombinant FVIII and FIX. These include chemical modification or creation of recombinant fusion proteins. Conjugation to hydrophilic polymers as polyethylene glycol (PEG) extends plasma half-life of FVIII or FIX decreasing their excretion and degradation.7-9 PEGylation can be random or site-specific and may employ PEG moieties of different molecular weight.10 Another chemical modification is the introduction of a disulfide bond between the light and the heavy chains of FVIII allowing for a single-chain FVIII molecule with a higher affinity to von Willebrand factor.11 Protein fusion technology is applied to produce recombinant factors fused to other proteins, such as the Fc fragment of IgG (rFVIII-Fc and rFIX-Fc) or albumin (rFIX). Fc- or albumin-fused factors have prolonged half-life by utilizing the neonatal Fc receptor (FcRn), that is expressed on various cell types and is responsible for endogenous IgG recycling into the circulation.12

As compared to standard rFIX, the modified rFIX products have shown half-life prolongations by 3-5 times that allow effective prophylaxis with once-weekly or even less frequent injections and may result in the maintenance of higher FIX trough levels.6 The half-life prolongation achieved with the new modified rFVIII is lower, but anyway, in the range of 1.5-1.8 times that of standard rFVIII products6 and it is ultimately limited by the half-life of VWF, the physiological chaperone of FVIII.11,13 Nevertheless, also these new rFVIII products may allow a reduction in the frequency of injections.

Safety and efficacy results are currently available for most of these modified FVIII and FIX products from specific clinical trials conducted in previously treated adults and children including the surgical use. Trials are still ongoing in previously untreated patients (PUPs). As demonstrated in phase III clinical trials, these new products allow to space factor injections for prophylaxis. This goal is fully achieved with new rFIX products that permit to maintain FIX levels well above 10 IU/dL with injections every 1-2 weeks.7,14 Also the success rate in bleeding control with a single infusion is high (80%-90%),7,14,15 The results concerning new rFVIII products indicate that prophylaxis regimens based on dosing every 3-5 days are effective8,9,16,17 and may be convenient and acceptable for a wider number of patients but it should be kept in mind that factor half-life is generally shorter in young children and therefore the recommended interval between doses is also shorter for children.6,12

Take Home Messages

- New modified recombinant factor VIII and IX products have been developed to extend factor half-life and improve prophylaxis regimens.
- Extended half-life factors allow for less frequent infusions, higher factor trough levels, or both.
- The impact on injection frequency or trough levels achieved with modified rFVIII is more modest as compared to new modified rFIX products.

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Overall, for both new rFIX and rFVIII products, data from phase III trials suggest that treatment tailored according to pharmacokinetic profile may improve the clinical outcome, particularly in terms of reduction of bleeding frequency and, maybe, factor consumption.

With respect to the safety results, no major issues have been raised to date, but post-licensing surveillance is important to establish long-term safety. The important aspect of immunogenicity was not problematic in PTPs but still require to be addressed in PUPS. The different manufacturing processes and characteristics of these new products imply that the safety profile should be specifically assessed for each of these agents. In particular, concerns have raised on the potential for accumulation after long-term exposures to PEG, although previous experiences with other PEGylated drugs were uneventful but commonly referred to short-term exposures.

Limited real-world data are currently available, mainly on the use of rFVIIIFc and rFIXFc. In Canada, 15 centers reported 139 patients transitioning to rFVIIIFc from rFVIII and to rFIXFc from rFIX; a reduction of factor utilization by 19% and 50%, respectively, was documented. Furthermore, data from one large pediatric program indicated that 45 children with severe hemophilia A reduced the number of infusions per week from an average of 3 to 2. Seven children with severe hemophilia B reduced the average number of infusions per week from 2.5 to 1. No development of inhibitors was observed following the switch.

More recently, a report from a single pediatric Center in USA described 36 patients who switched from standard rFVIII to rFVIIIFc (17) and from rFIX to rFIXFc and showed a reduction of their annual bleeding rate after treatment initiation from 2.3 to 1.3 and from 2.5 to 0.8, respectively. No inhibitor formation was reported.

### Future perspectives

Clinical trials on prophylaxis have shown dramatic reductions in bleeding rates; these observations have prompted the hemophilia community to advocate for a goal of “zero bleeds”. However, standard prophylaxis with its frequent intravenous injections has been demanding for many patients who are not able to maintain adherence long-term. The development and introduction of modified replacement products may have an impact on aspirations and expectations of what will be achievable with prophylaxis. Extended half-life factors allow for less frequent infusions, higher factor trough levels, or both. This is particularly the case with new rFIX while more modest impact on injection frequency or trough levels may be achieved with modified rFVIII. These new replacement agents may facilitate prophylaxis start at an earlier age without the need for central venous lines, allowing for more convenient dosing regimens and improved adherence. Moreover, they may favor patient switch from on-demand treatment to prophylaxis. Higher factor trough levels obtained with prophylaxis may lead to improved protection and fewer restrictions in activities.

In few conclusive words, improved clinical outcomes and quality of life seem to be within reach for hemophilia patients. Real-world data on a large scale are awaited to confirm the ambitious expectations nourished by the results of clinical trials.

### Table 1. New modified rFVIII and rFIX products.

| Molecule name         | Brand/generic name                  | Structure                          | Mean terminal half-life | Company              |
|-----------------------|-------------------------------------|-----------------------------------|-------------------------|----------------------|
| rFVIIIc10-12           | Elocet®/Eloct®                       | rBD-FVIII Fc fusion               | 19 h                    | Biogen and Sobi      |
| BAX 8554               | Adynovate®/Adynor®                   | PEGylated rFVIII (20 kDa)         | 14–16 h                 | Shire                |
| BAY 94-902712          | Damococog alpha pegol               | PEGylated rBD-FVIII (60 kDa)      | 19 h                    | Bayer                |
| N8-GP8                 | Turocog alpha pegol                 | GlycoPEGylated rBDT-FVIII (40 kDa) | 18–19 h                 | Novo Nordisk         |
| rVIII-SingleChain16    | Afsyla®                             | Single chain rFVIII               | 13 h                    | CSL Behring          |
| rF00C15                | Alprolix®                           | rIXFc fusion                      | 82 h                    | Biogen and Sobi      |
| CSL654 (rIX-FP)14      | Idelvion®                           | rFIX album fusion                 | 102 h                   | CSL Behring          |
| N9-GP5                 | Refixa®/Refinyn®                     | GlycoPEGylated rFIX               | 93 h                    | Novo Nordisk         |

| FK, factor Fc; FVIII, factor VIII; PEG, polyethylene glycol; rBD, recombinant B-domain deleted; rBDT, recombinant B-domain truncated; rFVIII, recombinant factor VIII; rFIX, recombinant factor IX; Sobi, Swedish Orphan Biovitrum AB. |

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