The New landscape of Therapeutics for the Treatment of Hemophilia

Introduction

There have been many changes to the treatment landscape of Hemophilia over the past few decades. Initial therapy with blood products was replaced with plasma-derived lyophilized factor concentrates, which allowed for home infusion and improved quality of life. Further purification and viral inactivation processes increased the safety profile of plasma-derived concentrates. Genetic cloning of factors VIII and IX in the 1980’s and 1990’s has led to the production of recombinant products.

High cost of therapy, the frequency of infusions often requiring venous access devices, and inhibitor formation have been issues that have impacted effective prophylaxis. Further advances in product half-life extension through different technologies including albumin or neonatal Fc fusion, PEGylation, and single chain technology have led to the recent FDA approval of four extended-half-life recombinant products, with several other products in late-stage clinical trials. The manufacturing of several recombinant products (Nuwiq, Eloctate, Alprolix) in Human Embryonic Kidney (HEK) cell lines may result in a product that is more like the human native protein in regards to post-translational modifications. Several nonfactor therapeutic approaches with improved ease of administration are being explored. The hope for gene therapy is on the horizon; however, issues impacting achieving long-term stable factor expression, potential risk of insertional mutagenicity, and hepatic toxicity remain.

The Generations of Recombinant Factor Products

Initial recombinant FVIII products contained added human albumin as a stabilizer. Third generation products eliminated human and animal proteins from the culture media and final preparation, and utilized additional viral inactivation steps to further increase safety. FDA approval of Alprolix in March 2014, Eloctate in June 2014, and Nuwiq in September 2015 ushered in the fourth generation of products which are produced in Human Embryonic Kidney (HEK) cell lines, without human or animal protein exposure. It is hoped that these products more closely resemble the native clotting factor and therefore may impact the recognition of the protein by the immune system and potentially translate into a decreased rate of inhibitor development, especially in FVIII deficiency – time will tell.

Table 1: Generations of Recombinant Factor Products

<table>
<thead>
<tr>
<th>Generation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>1st</td>
<td>Contains albumin in final preparation, exposed to human or animal proteins during production</td>
</tr>
<tr>
<td>2nd</td>
<td>No albumin in final preparation, exposed to human or animal proteins during production</td>
</tr>
<tr>
<td>3rd</td>
<td>No human or animal protein exposure</td>
</tr>
<tr>
<td>4th</td>
<td>Produced in a human cell line, no human or animal protein exposure</td>
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B Domain Modification in FVIII Recombinant Products

The FVIII gene is a large molecule. B-domain modification through deletion or truncation improves production efficiency. Once activated, the B domain deleted or truncated protein is the same as the activated native protein. Currently licensed products that have undergone B-domain modification include Xyntha (Pfizer), Novoeight (Novo Nordisk), Nuwiq (Octapharma), Eloctate (Biogen), and OBIZUR (Baxalta). (See Figure 1, next page.)
New Recombinant Factor Product Concentrates

The following sections will discuss recombinant products that have been recently licensed or are in late-stage clinical trials. Other recombinant products that were licensed and launched in the United States prior to 2013, or are in earlier stages of development or clinical study will not be reviewed.

New Standard Half-Life Recombinant Factor Concentrates:

Factor VIII Deficiency (Hemophilia A)

Novoeight (Turoctogog Alfa):
Novoeight is a third generation B-domain deleted recombinant product manufactured by Novo Nordisk in the Chinese hamster ovary cell line (CHO). It was launched in the United States on March 26, 2015. Median annualized bleeding rate (ABR) was reported as 3.1 in 213 subjects receiving Novoeight for routine prophylaxis. It is approved for prophylaxis and on-demand treatment of bleeding episodes in children, adolescents, and adults with Hemophilia A.14,16,17 Kovatry (Octocog Alfa):
Kovatry is a third generation full length recombinant FVIII product produced in a Baby Hamster Kidney (BHK) cell line. The FDA approved Kovatry in March 2016 for use in adults, adolescents, and children with Factor VIII deficiency. Several improvements have been reported with Kovatry in comparison to its predecessor, Kogenate (rFVIII-FS), including improvements in consistency of glycosylation and expression. Furthermore, coexpression of human heat-shock protein 70 (HSP70), a molecular chaperone involved in the proper folding of proteins and prevention of protein aggregation, enhances the viability of the expression cell line by inhibiting apoptosis and possibly by increasing proper folding of the FVIII protein. LEOPOLD II, Compared to the thrice weekly group, patients in the twice weekly group had ABR during the first 6-month period of treatment, but the ABR was comparable between the two groups in the second 6-month period.14,15,16

Factor IX Deficiency (Hemophilia B)

ixixnity (Trenaracog Alfa):
ixixnity is a third generation recombinant antihemophilic Factor IX produced in a Chinese hamster ovary cell line (CHO). It is manufactured by Emergent Biosolution, and was FDA approved on April 29th, 2015. Ixixnity is licensed for prophylaxis and on-demand treatment of bleeding episodes in adults and adolescents with Hemophilia B.16,17

Von Willebrand Factor Deficiency

Vonvendi
Vonvendi (Vonicog Alfa) is a recombinant Von Willebrand Factor (VWF) that was FDA approved in December 2015 for on-demand treatment of bleeding episodes in adults > 18 years of age with all subtypes of Von Willebrand Disease (VWD). It is a third generation product manufactured in a CHO cell line. A total of 193 bleeding episodes were reported in 22/37 patients with VWD exposed to Vonvendi. Out of these patients, 4 had type 2A, 1 had type 2N, and 17 had type 3 VWD.18,19 The normal expected plasma half-life of FVIII is 2-12 hours, and 18-24 hours for FIX. Utilizing current technologies, rFVIII plasma half-life can be effectively increased to 4-5 times the standard half-life. The results of rFVIII half-life prolongation have been more modest at 1.4-1.5 times the standard half-life, likely related to the dependence of FVIII half-life on the binding and clearance of endogenous von Willebrand factor.21 Notably, product half-life is often inversely proportional to patient age, with the pediatric population demonstrating increased clearance rates and volume of distributions.

Figure 1:

New Standard Half-Life Recombinant Factor Concentrates:

Figure 2:

Extended Half-Life (EHL) Factor Concentrates

Despite the advent of recombinant factor concentrates, hemophilia patient outcomes have remained suboptimal; the frequency of required infusions impacts quality of life, many patients require central venous access devices for continued venous access, and most patients with hemophilia spend the majority of time with factor trough levels below the mild deficiency range. These therapeutic issues have sparked investigation into development of products with an extended half-life. The technologies that have been applied to recombinant FVIII and FIX products include neonatal Fc receptor (FcRn) and albumin fusion, and PEGylation. In the case of recombinant FVIII, Single Chain technology has also been employed.24


Eloctate (rFVIIIFc)
Eloctate is a fusion protein composed of B-domain deleted recombinant factor FVIII and the Fc portion of IgG1. It is a fourth generation product produced from a HEK cell line and is manufactured by Biogen. It was the first EHL rFVIII product to be FDA approved in 2014. Pharmacokinetic studies have reported an approximate half-life of 19.7 hours in adults and 12.7-16.4 hours in children and adolescents.26 Safety and efficacy has been demonstrated in the adult and
Utilizing a process that ensures 60% of PEG chains are located in the B-domain, which are subsequently cleaved upon activation. Adynovate was U.S. FDA approved on November 13, 2015 for prophylaxis and on-demand therapy. A pivotal phase III trial of 175 patients receiving prophylaxis and 12 patients receiving on-demand therapy, the ABR was 1.3 and 30.9, respectively.39

Single Chain Technology: rVIII-SingleChain (CSL-627) rVIII-SingleChain is produced through Single Chain Technology, which covalently links heavy and light chains within a single V88I chain to increase binding affinity to Von Willebrand Factor. The prolonged VWF half-life is then utilized to provide longer V88I half-life through decreased clearance and larger area under the curve. In a pivotal phase I/III trial of adults with severe Hemophilia A, 173 patients were followed with 146 receiving prophylaxis with a resultant median ABR of 1.66.6 Initial data from Phase I trials revealed a half-life of approximately 13.1 hours in adults, not very dissimilar to that reported with standard half-life recombinant factor VIII products. An open-label multicenter phase III study is currently underway (NCT 02172950).

OBIZUR is a recombinant porcine sequence FVIII product licensed for treatment of acquired Hemophilia A (autoimmune FVIII inhibitors). The B-domain is naturally present in naturally occurring porcine factor VIII has been replaced with a twenty-four amino acid linker. Once activated, the resulting rpFVIII has a comparable activity to the endogenous human FVIII. Obizur is expressed in a genetically engineered baby hamster kidney (BHK) cell line. The acquired FVIII antibodies often have decreased cross-reactivity to this protein, and therefore it can be used to achieve hemostasis with the added ability to measure FVIII levels through standard assays. Monitoring of levels and for development of anti-porcine factor VIII antibodies is recommended.

Gene Therapy
Work on development of viable Gene therapy, in particular for Hemophilia B, has continued with the hopes of the potential covalently attached to a 40-kDa PEG molecule. It is manufactured by Novo Nordisk, and has been submitted for licensure to the FDA. In a phase III study of adults, 15 patients chose on-demand therapy and 59 patients chose prophylactic therapy. The patients who chose prophylaxis were randomized to receive either 10 IU/kg or 40 IU/kg weekly; the half-life was reported as approximately 92 hours. The ABR for on-demand therapy was 16, whereas the ABR for the prophylaxis groups with 10 IU/kg weekly and 40 IU/kg weekly were 3 and 1, respectively. In 25 previously treated pediatric patients, N9-GP has found to have a half-life of 69.6-73.6 hours.49 A Phase III trial investigating the safety and efficacy of N9-GP in previously untreated patients (ParadigmTM6, NCT 02141074) is currently underway.

The Future of Extended Half-Life Products
Recent FDA approval of several extended half-life factor concentrates with others in late stage clinical trials has sparked debate on patient and product selection, with particular emphasis on potential risks and benefits. Extended half-life products may reduce the number of required infusions in patients with severe hemophilia, with the potential to decrease need for placement of venous access devices and perhaps ‘needle phobia’. These products may allow the ability to achieve consistently higher trough levels, with the potential to prevent breakthrough bleeding and subsequent joint disease. Animal models have suggested decreased inhibitor rates in EHL product use; if this data is demonstrated in humans, then these products could improve disease-related morbidity and mortality. This must be proven through clinical studies. Higher endogenous Von Willebrand Factor levels in older adults may translate to longer half-life of EHL rVIII products. Conversely, the pediatric population may theoretically derive less benefit from rFVIII EHL products in terms of half-life extension. Monitoring continues to be important in both pediatric and adult populations. Given the current plethora of available products, it is important to personalize patient care with consideration of all risks and benefits.

Inhibitor Formation
The prevalence of inhibitor formation in previously untreated patients is approximately 30% in severe Hemophilia A, and up to 5% in severe Hemophilia B. Complications of inhibitors include failure of standard replacement therapy with difficulty achieving hemostasis, increased morbidity and mortality, and significantly increased surgical risk. Inhibitors remain one of the most severe complications of hemophilia, and are associated with an increased economic burden.52 Treatment includes instituting a bypassing agent to achieve hemostasis in bleeding episodes, as well as immune tolerance induction therapy to eradicate the inhibitor as appropriate.53,54,55 Per the SIPPET trial presented at ASH 201556, rFVIII products were found to be associated with a 1.87-fold higher incidence of inhibitors than the plasma-derived FVIII class that also included WVF. This difference remained even when second generation full length rFVIII concentrates were excluded from the analyses, suggesting that the presence of WVF in the concentrate may have a protective effect. The final publication is awaited for a more detailed analysis of this data. The trial did not include the newest generation of products and these therefore will warrant further study. How this trial will impact care paradigms in pediatric patients has yet to be determined.

Recombinant FvIII (NovoSeven RT) and plasma-derived activated prothrombin complex concentrate (FEIBA) are FDA approved for the purpose of achieving hemostasis in patients with inhibitors to FVIII or FIX. OBIZUR is a recombinant porcine sequence FVIII product licensed for treatment of acquired Hemophilia A (autoimmune FVIII inhibitors). The B-domain normally present in naturally occurring porcine factor VIII has been replaced with a twenty-four amino acid linker. Once activated, the resulting rpFVIII has a comparable activity to the endogenous human FVIII. Obizur is expressed in a genetically engineered baby hamster kidney (BHK) cell line. The acquired FVIII antibodies often have decreased cross-reactivity to this protein, and therefore it can be used to achieve hemostasis with the added ability to measure FVIII levels through standard assays. Monitoring of levels and for development of anti-porcine factor VIII antibodies is recommended.

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Alprolix is composed of rFIX fused with the Fc domain of IgG1. It is a fourth generation product produced in a HEK cell line, and is manufactured by Biogen. The reported half-life is 87 hours in adults, and varying from 63-83.59 hours in the pediatric population. In A Phase III nonrandomized study of patients >12 years of age with hemophilia B (FIX activity <2 IU/dL), the following treatment groups were evaluated: 1) 50 IU/kg weekly; 2) 100 IU/kg every 10 days; and 3) on-demand therapy. The ABR in the three groups was 3.1, 2.4, and 18.7, respectively.33,34,35

N8 GP (Turoctocog Alfa Pegol)
N8 GP is a third generation product produced through site-specific glycoPEGylation of B-domain truncated recombinant FVIII. It is manufactured by Novo Nordisk and is awaiting FDA licensure. N8 GP has a reported half-life of approximately 18.6-19.5 hours in adults.38 A Phase II/III study in 134 previously treated patients >12 years of age demonstrated preservation of full biologic activity with annual bleeding rate (ABR) ranging from 1.9 to 4.1 in patients receiving prophylaxis and 23 for patients receiving on-demand therapy. The Future of Extended Half-Life Products
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Conclusions

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