Kogenate® FS: antihemophilic factor rFVIII-FS

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Characterization of the factor VIII (*FVIII*) gene and expression of factor VIII through recombinant technology paved the way for the availability of recombinant factor VIII (rFVIII) for intravenous infusion, a significant breakthrough in the treatment of hemophilia A. Kogenate® FS (rFVIII-FS) is a native, full-length factor VIII molecule, produced from a baby hamster kidney cell line, purified and formulated without the addition of albumin, and stabilized with sucrose. Licensed in the USA and the EU in 2000, the hemostatic efficacy and safety (low rate of adverse events, viral safety and low incidence of inhibitors) have been consistently demonstrated through clinical trials and postmarketing studies. Accumulated evidence supports the use of rFVIII-FS for on-demand and prophylaxis treatment regimens, continuous infusion for surgeries or severe bleeding episodes, and immune tolerance induction for treatment of persistent inhibitors.

Keywords: factor VIII, hemophilia A, Kogenate® FS, sucrose-formulated recombinant factor VIII

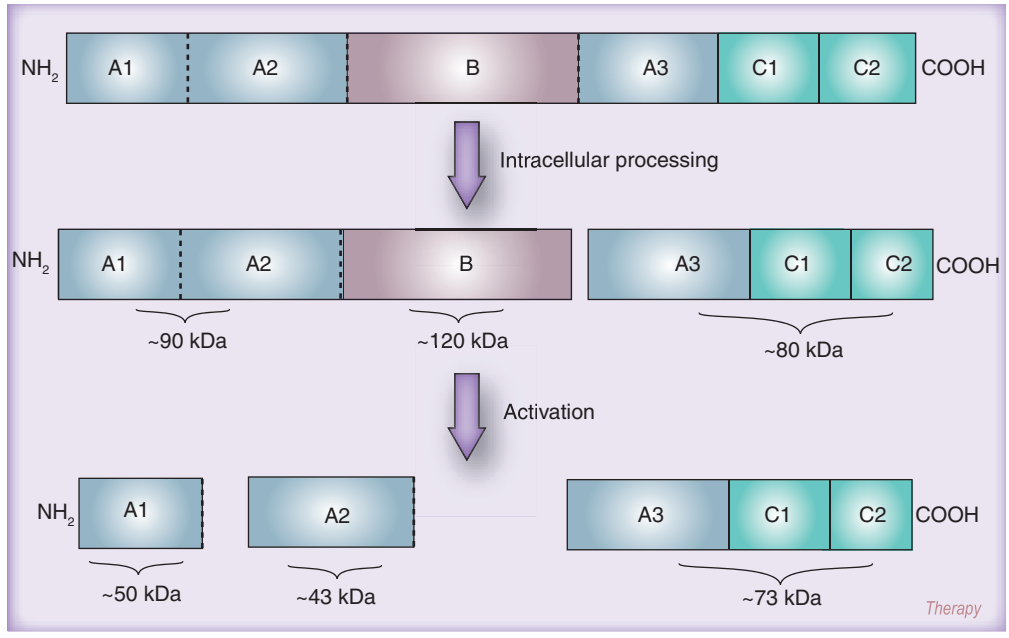
Future Drugs Ltd

The World Federation of Hemophilia (WFH) estimates that 1 in every 10,000 people is born with hemophilia A [101], with approximately 400,000 individuals affected worldwide. This inherited bleeding disorder is associated with the absence or insufficient production of factor VIII (FVIII), an important element of the coagulation cascade; disease severity ranges from mild to severe, based upon the level of FVIII clotting activity in the blood (severe: <0.01 IU/ml; moderate: 0.01–0.05 IU/ml; mild: 0.05–0.40 IU/ml) [101]. Disabling arthropathy can develop as a result of repeated hemorrhages into muscles and joints. Intracranial hemorrhages can be life threatening. Replacement therapy with FVIII is an essential component of the health and quality of life of hemophilia patients. In the early 1980s, many severe hemophilia patients were found to have blood-borne viral infections associated with the use of plasma-derived (pd)FVIII [1], and this unfortunate situation provided great impetus for improvements in donor screening/selection practices and manufacturing processes, ultimately resulting in tremendous improvement in the safety of therapeutic agents for the hemophilia population. Although more expensive than plasma-derived FVIII products, recombinant (r)FVIII products have the inherent safety benefit of eliminating dependence on pooled human plasma. As a result of this advantage with respect to viral transmission safety, the Medical and Scientific Advisory Committee (MASAC) of the National Hemophilia Foundation recommended the use of recombinant clotting factors and has urged the conversion from plasma-derived concentrates to recombinant products [2]. Kogenate® formulated with sucrose (FS; rFVIII-FS; Bayer HealthCare) is a full-length rFVIII produced from a baby hamster kidney (BHK) cell line. In contrast to Kogenate (rFVIII-BHK, the first of the rFVIII product line from Bayer), rFVIII-FS is purified and formulated without the addition of albumin and is stabilized with sucrose. Additionally, the manufacturing process includes solvent/detergent viral inactivation for improved viral safety.

Chemical profile

Characterization of the *FVIII* gene, expression of FVIII from recombinant DNA clones and detailed amino acid analysis of the FVIII protein were technological developments that made commercial production of rFVIII possible [3–6]. The *FVIII* gene (located on the X chromosome) is 186,000 bp, and consists of 26 exons. The 9000-bp mRNA codes for a protein of 2351 amino acids, which is secreted as a 2332-amino acid protein following N-terminal processing and glycosylation (approximately 300,000 Da molecular weight). The FVIII protein consists of three types of domains (three homologous A domains, two homologous C domains, and the B domain; arranged A1-A2-B-A3-C1-C2), shown schematically in **Figure 1**. Intracellular processing and extracellular thrombin cleavages

Figure 1. Simplified schematic of FVIII protein and activation



result in active FVIII, a heterotrimer of polypeptides 50,000 (A1), 43,000 (A2) and 73,000 (A3-C1-C2) Da. It is this heterotrimer that functions at a critical step in the intrinsic coagulation cascade, enhancing Factor X activation by Factor IXa.

rFVIII-FS production utilizes a BHK cell line transfected with the gene for human FVIII. This stable and well-characterized cell line produces glycosylated full-length protein with the functionality of natural FVIII. The manufacturing process for rFVIII-FS involves fermentation and extensive purification, as outlined in **Figure 2**. rFVIII-FS is produced from the BHK cell line in deep tank continuous perfusion fermenters, without the addition of fetal calf serum or other bovine products in the production process. rFVIII obtained from the conditioned culture fluid undergoes an extensive purification process, including 6-step column chromatography and viral inactivation.

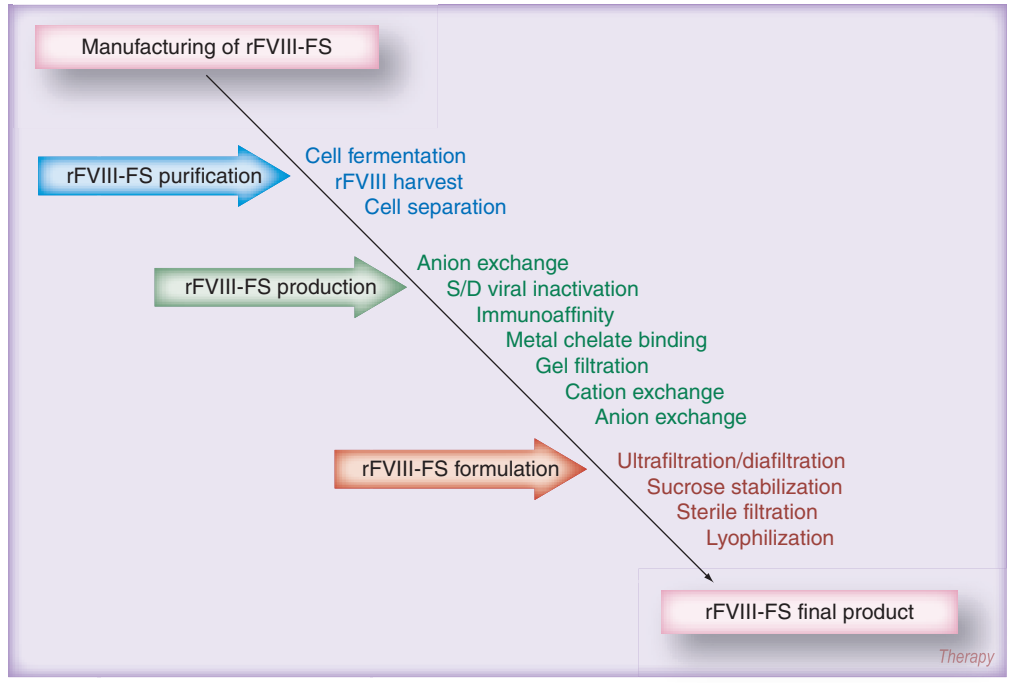
In contrast to the process for its predecessor product, rFVIII-BHK, rFVIII-FS is produced without the addition of albumin during purification and during final formulation of the protein, solvent/detergent viral inactivation is incorporated into the process, and improved purification steps have been included. One diluent volume size (2.5 ml) is used for all dosage forms of rFVIII-FS. Contamination of rFVIII products with viruses of concern for the blood/plasma supply is considered extremely unlikely. Nonetheless, due to the theoretical risk of viral contamination, the rFVIII-FS manufacturing process includes solvent/detergent viral inactivation. Experimental studies with production material spiked with model viruses representative of a broad range of theoretical contaminants in source materials have shown reduced viral load for many of the process steps, including solvent/detergent inactivation, immunoaffinity chromatography and eluate hold steps [7]. Additionally, *in vivo* and *in vitro* test systems have been utilized to demonstrate the removal of transmissible spongiform encephalopathy infectivity during the rFVIII-FS manufacturing process [8–11].

Preclinical safety & efficacy studies

Preclinical studies have provided pharmacokinetic, toxicological and biological data in support of the safety, tolerability and efficacy of rFVIII-FS [7,12]. *In vivo* efficacy was assessed in hemophilic dogs by measuring cuticle bleeding times and activated partial thromboplastin time (aPTT) following infusion of rFVIII-FS. Improvement in aPTT and correction of bleeding showed similar efficacy as previously demonstrated with rFVIII-BHK and plasma-derived FVIII in this same model system [12,13].

Acute toxicity studies of rFVIII-FS have been conducted in mice, rats and rabbits, and subacute toxicity studies in rabbits and dogs. No adverse effects with respect to body weight gain, blood chemistry, necropsy or histopathology were found

Figure 2. Manufacturing process for rFVIII-FS.



rFVIII-FS: Recombinant factor VIII formulated with sucrose.

for any of these studies [12]. Pharmacokinetic studies in rabbits with rFVIII-FS showed similar plasma clearance (CL), terminal half-life ($t_{½}$), maximum plasma concentration (C_{max}), AUC and volume of distribution at steady state (V_{ss}) values compared with rFVIII-BHK. Hyperimmunization of rabbits with rFVIII-FS was conducted in order to evaluate the development of antibodies reactive to possible neoantigens on the new recombinant protein [12]. This immunogenicity model was developed originally to compare rFVIII-BHK with plasma-derived FVIII for novel epitopes on the recombinant protein [14]. Antibodies unique to the rFVIII-FS molecule were not detected (i.e., antibodies generated following immunization with rFVIII-FS showed similar binding to rFVIII-FS, rFVIII-BHK or plasma-derived FVIII), similar to the results of the original study comparing rFVIII-BHK with plasma-derived FVIII.

Clinical development of rFVIII-FS

Previously treated patients

The initial clinical investigation of rFVIII-FS was conducted in previously treated patients (PTP; ≥100 prior exposure days) with severe (<2% FVIII) hemophilia A in both North America and Europe. Together, these multicenter studies can be divided into four stages. Stage I consisted of a randomized safety and pharmacokinetic evaluation comparing rFVIII-FS with rFVIII-BHK. Stages II (4 weeks of regular infusions, three-times per week) and III (6 months of the patient's usual dosage and dosage regimen) assessed the efficacy and safety of rFVIII-FS for home therapy. Stage IIIS recorded hemostatic efficacy in patients durin surgery and the postoperative period. Stage IIIE assessed the efficacy and safety of rFVIII-FS over an 18–24-month period.

Pharmacokinetic parameters for rFVIII-FS for Europe and North America were similar [15,16]. The North America data demonstrated bioequivalence of rFVIII-FS and rFVIII-BHK; pharmacokinetic parameters of the European population were similar to both rFVIII-BHK and rFVIII-FS in the North Americn study. Data from 19 North American patients evaluated at 24 weeks (repeat pharmacokinetic and recovery analyses) showed both a consistent pharmacokinetic profile and *in vivo* properties over a 6-month treatment period.

Stages II/III/IIIE evaluated the safety and efficacy of rFVIII-FS treatment in 71 patients (both European and North American) during home therapy over a time period greater than 18–24 months [15]. A total of 12,546 infusions (on-demand and prophylaxis) were administered to these patients, for a cumulative total of 11,867 exposure days (EDs). Out of 2585 bleeds, 93.5% were treated with one or two infusions, and

80.5% of responses were rated as excellent or good (**Figure 3**). Adverse events were associated with less than 2% of infusions and 0.27% of infusions were associated with an event rated as only remotely likely to be drug-related.

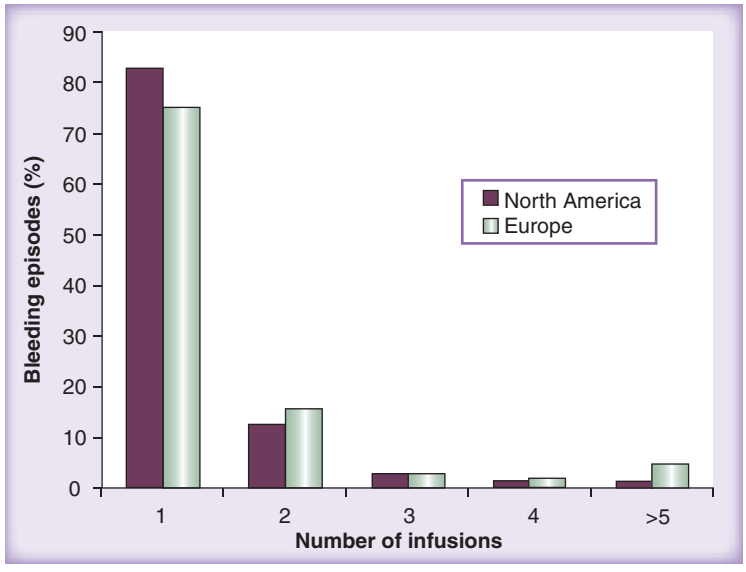
Stage IIIS confirmed the hemostatic efficacy of rFVIII-FS during surgical procedures in PTPs. A total of 22 surgical procedures (21 elective and one emergency) were performed in 15 patients during a period of 24 months. Hemostasis was judged as either excellent (16) or good (6) by the attending physicians for the various procedures, which ranged from major to minor surgeries [17].

Additional support for the safety and efficacy of rFVIII-FS was demonstrated in a three-part Japanese clinical study in 20 PTPs with moderate (n = 5) or severe (n = 15) hemophilia A. The study included a comparison of the pharmacokinetics of rFVIII-FS and rFVIII, a 4-week safety and efficacy assessment of prophylactic treatment, and evaluation of the safety and efficacy of on-demand rFVIII-FS treatment over 24 or more weeks [18,19].

Previously untreated patients/minimally treated patients

A 2-year, international, open label, non-controlled investigation evaluated the safety and efficacy of rFVIII-FS in previously untreated patients (PUPs) and minimally treated patients (MTPs) with severe hemophilia A [20]. A total of 61 PUPs and MTPs with severe hemophilia from 32 treatment centers in Europe and North America were treated with 753,970 IU of rFVIII-FS during this 2-year clinical investigation. Of 1178 bleeding episodes, hemostasis was achieved with one or two infusions in 89.2% of all bleeding episodes (68% of bleeding episodes were rated as severe). Thirteen adverse events in ten patients (13/750 or 1.7%) were assessed with an 'at least possible' relationship to study drug. These included ten reports of inhibitor formation in nine patients. No evidence of viral transmission through rFVIII-FS was observed.

Figure 3. Efficacy of rFVIII-FS during home therapy.



rFVIII-FS: Recombinant factor VIII formulated with sucrose.
Data from [15].

Safety & tolerability

Inhibitors

The development of a FVIII inhibitor (antibodies inhibiting FVIII activity) from FVIII replacement therapy is a serious complication for hemophilia patients. Severity of disease, the genetic mutation responsible for hemophilia, family history of inhibitors, ethnicity, molecular modifications of the FVIII molecule during the manufacturing process, and the number of EDs to FVIII are among the known or suspected risk factors for the development of FVIII inhibitory antibodies. The risk for inhibitor development was evaluated in the prospective studies described above. For the 71 PTPs with severe hemophilia treated with rFVIII-FS during home therapy (mean for North America: 125 EDs, mean for Europe = 216 EDs), there was no *de novo* inhibitor formation. Consistent with recommendations of the FVIII and FIX Subcommittee of the International Society of Thrombosis and Haemostasis' Scientific & Standardization Committee, and the European Agency for the Evaluation of Medicinal Products to use PTPs as the preferred population (as opposed to PUPs) in which to evaluate product immunogenicity [21,22], these results support the lack of product-related immunogenicity with rFVIII-FS.

In the PUPs/MTP study, 37 PUPs and 23 MTPs were evaluable for inhibitor analysis, and 15% (9/60) of these patients developed an inhibitor titer of at least 0.6 Bethesda units (BUs) during the study. Mutation analysis of the patient population in this study showed that these individuals were at high risk for inhibitor formation [20,23]. Inhibitors were identified in the nine patients (five PUPs and four MTPs) after a median of 9 exposure days. Six had inhibitor titers greater than 5 BU (high titer), and three patients had low titer inhibitor values, of which two were transient in nature. By comparison, the inhibitor incidence reported in PUPs with severe hemophilia treated with other rFVIII products (including rFVIII-BHK) is approximately 30% [24–26].

Adverse events

Administration of rFVIII-FS to severe hemophilia patients in both the PTP and PUP studies was well tolerated. During home therapy of PTPs, drug-related adverse events were observed in 0.27% of 12,546 infusions. Specific events were recorded as mild or moderate, with the exception of one patient who developed palpitations (categorized as severe) that resolved following analgesic treatment (this patient had a 2-year history of these symptoms prior to participation in the study). Treatment with rFVIII-FS was not discontinued for any patient as a result of adverse events. Evaluation of immune responses to murine, BHK or rFVIII protein consisted of an enzyme-linked immunosorbent assay (ELISA) of plasma samples obtained at intervals throughout the study. No clinically significant responses were detected. No seroconversions for HIV, hepatitis B or C were observed. For seven patients, hepatitis A seroconversion was attributed to vaccination during the study period.

Adverse events for PUPs/MTPs treated with rFVIII-FS rated as 'at least possibly' drug-related were 0.14% or one out of 723 infusions. ELISA assay of plasma samples for immunoglobulin (Ig)G antibodies formed to trace mammalian proteins showed that five patients with inhibitors detected by Bethesda assay developed anti-rFVIII IgG and three of these patients developed antibodies to murine IgG. Transient elevations in antibodies to rFVIII (3), murine IgG (7) and BHK protein (1) were detected, but there were no related adverse events. Monitoring for viral safety shown no seroconversions (except in association with vaccination), and no evidence of viral transmission associated with rFVIII-FS treatment.

Postmarketing studies

Following the approval of Kogenate FS in the USA and the EU in 2000, numerous studies have expanded upon the safety and efficacy data for this rFVIII product.

Surveillance studies

Safety of rFVIII-FS was evaluated in a European multicenter, post-licensure, observational study of routine treatment of severe hemophilia patients (<2% FVIII:C) for up to 24 months of therapy. Data reported from an interim analysis (12 months of observation) for 202 patients (mean of 98.6 EDs) from nine countries, included a total of 23,213 infusions overall during this observation time frame [27]. A total of 40 adverse events were reported for 17 patients, none related to rFVIII-FS replacement therapy. No *de novo* inhibitors were detected in samples from patients with at least 20 EDs. Two patients were reported to have *de novo* inhibitor development: a 9-month-old PUP developed a 20 BU inhibitor after 15 EDs; and a 19-month-old, with less than 20 ED at study entry, developed a low titer inhibitor, 2.2 BU, after 9 EDs to rFVIII-FS. A third patient had a low titer assay result that could not be confirmed with retesting, and there were no clinical signs of an inhibitor, therefore this was considered to be a false positive.

As a consequence of the serious ramifications, monitoring for inhibitor development is an important and ongoing element of FVIII replacement therapy. A subcommittee of the Association of Hemophilia Clinic Directors of Canada (AHCDC) has evaluated the conversion of Canadian hemophilia patients from rFVIII to rFVIII-FS. Patient blood samples were evaluated for the presence of inhibitors by the Bethesda assay (Nijmegen modification) at baseline and 12 and 24 months following conversion to the new product. Results of this study showed that no inhibitors were detected in 12- or 24-month post-switch samples among patients with negative baseline values. Only patients with pre-existing inhibitor titers at baseline (prior to the switch to rFVIII-FS) had inhibitors in 12- or 24-month samples [28].

A retrospective chart review was conducted of Irish hemophilia patients who were switched from using rFVIII produced from a Chinese hamster ovary (CHO) cell line to rFVIII-FS for replacement therapy [29]. Most patients (94.6%) in this study had greater than 100 EDs prior to the product change, and most (89.2%) had severe hemophilia (≤1% FVIII:C). For up to 20 months following the switch, plasma samples were collected for inhibitor analysis (Bethesda assay with Nijmegen modification) as part of routine clinic visits. Of the 93 patients who were switched to rFVIII-FS, 16 had a history of an inhibitor. Three patients with pre-existing inhibitors had transient, low titer inhibitors detected in plasma samples during the observation period of the study. One patient (who had moderate hemophilia, >100 EDs) without prior inhibitor history developed a *de novo* inhibitor (1.0 BU) following the switch from rFVIII-CHO to rFVIII-FS. This single positive inhibitor assay appeared following high-dose treatment for a surgical intervention, and then resolved. All subsequent assays during the observation period were negative.

Collectively, the results of these surveillance studies are consistent with prelicensure studies, and support the safety and low risk of inhibitor development associated with the use of rFVIII-FS.

Immune tolerance induction

For patients with persistent inhibitors (particularly high titer), routine on-demand or prophylactic treatment with FVIII becomes ineffective in controlling bleeds. Immune tolerance induction (ITI) involves frequent, high-dose FVIII exposure in an effort to create tolerance to the exogenously administered FVIII. While the approach to ITI is not standardized, and consensus on the optimal protocol is lacking, there is good evidence (albeit in uncontrolled studies) to suggest that ITI is effective, with success rates of 70–80% or greater in some reports [30–32]. rFVIII-BHK and rFVIII-FS have been used successfully in ITI protocols. A retrospective study from five Canadian hemophilia treatment centers was conducted that included data obtained from 32 patients (30 with severe hemophilia and two mild) on ITI from 1994–2003 [33]. A total of 29 patients completed ITI after a median of 1.1 years treatment, with a successful outcome for 23 (79.3%) patients. Success criteria for 12 patients included a negative inhibitor assay, normal recovery and normal half-life. For four patients, a negative inhibitor assay and normal FVIII recovery defined success, and a negative inhibitor assay was the only index of success for six patients. rFVIII was used exclusively for 25 patients, and four patients used plasma-derived FVIII exclusively or plasma-derived FVIII followed by rFVIII for ITI. Nineteen of the 25 patients treated only with rFVIII for ITI had successful outcomes [33].

Prophylaxis

Chronic arthropathy is a debilitating consequence of recurrent joint bleeds, and most common in patients with severe hemophilia. Because of evidence from a large number of mostly retrospective and/or uncontrolled studies that demonstrated the advantages of prophylaxis started at an early age [34–38], the Medical and Scientific Council of the National Hemophilia Foundation has advised implementation of prophylaxis as optimal therapy for persons with severe hemophilia A [39]. Early initiation of prophylaxis (before onset of frequent bleeds) is recommended with the goal of keeping trough levels of FVIII above 1%. Recently, the results from a prospective, randomized, controlled, multiyear study designed to evaluate the effectiveness of prophylaxis on joint outcome have been presented by Manco-Johnson and colleagues [40]. This study was started using rFVIII-BHK and later used rFVIII-FS. Young boys with hemophilia A (with no more than two hemorrhages per index joint) were randomized to either prophylaxis (25 U/kg every other day) or enhanced on-demand therapy (>3 infusions, totaling >80 U/kg for acute joint bleeds). At 6 years, joint status was evaluated by MRI and x-ray of index joints (primary outcome). Secondary outcomes included joint function based on a physical exam scale [41], number of hemorrhages, and factor utilization. At 6 years, boys randomized to the prophylaxis group had significantly fewer hemorrhages per year and showed improved joint function compared with children treated with enhanced on-demand therapy, supporting the effectiveness of prophylaxis with rFVIII-FS.

Continuous infusion

Administration of FVIII by continuous infusion may offer advantages over bolus administration for surgeries and the treatment of severe bleeding episodes. Stability of plasma FVIII levels (fewer peaks and troughs), increased safety, reduced factor consumption, and reduced transfusion requirements are among the advantages associated with continuous infusion [42,43]. Issues of concern regarding continuous infusion of FVIII include stability of the FVIII preparation, contamination/sterility of reconstituted factor, thrombophlebitis, and potentially inhibitor formation. The stability of rFVIII-FS for use in continuous infusion was demonstrated *in vitro* [44]. Successful use of rFVIII-FS by continuous infusion has been reported for surgeries by Viswabandya and colleagues and Luboshitz and colleagues [45–47]. Combined, these studies represent surgeries on 24 patients, with excellent hemostasis, and without perioperative complications.

Product choices & reconstitution systems

Kogenate FS is one of five currently marketed rFVIII products in the USA. All of these products are considered safe and equally effective for FVIII replacement therapy, yet there are differences that distinguish them [48–52]. In addition to product safety, the ease, simplicity, and safety (particularly exposure to needles) of FVIII reconstitution and infusion are important issues for hemophilia

patients and caregivers. Several reconstitution systems have been developed to simplify the traditional vial-to-vial reconstitution method and minimize the risk of needlestick injury [53]. rFVIII-FS with BioSet® [53] is a self-contained, needleless reconstitution system with a prefilled diluent syringe for reconstitution without exposed needles. A study by Butler and colleagues showed that nurses, patients and caregivers preferred BioSet to a plastic double-spike reconstitution device or conventional vial-to-vial reconstitution on nine ranking items, which included [53]:

- Ease of use
- Safety from needlesticks
- Speed of reconstitution
- Storage convenience
- Ease of teaching the method
- Amount of waste
- Convenience for traveling,
- Ease of learning the method
- Overall preference

An ongoing, international, observational, postmarketing study is evaluating patient satisfaction and preferences compared with previous infusion methods for patients who converted to rFVIII-FS with BioSet. An analysis of data collected to date for German patients with hemophilia (n = 77 completed the study) has been presented recently [54]. The results of the German cohort showed that most patients (>90%) preferred the BioSet reconstitution system compared with their previous method.

Conclusion

rFVIII-FS is a recombinant product for the treatment of hemophilia A that is purified and formulated without plasma-derived blood products. The production process includes viral inactivation/elimination steps, for an added margin of safety. North American pharmacokinetic studies demonstrated bioequivalence between rFVIII-FS and its predecessor recombinant product, and by extension, with plasma-derived FVIII. Clinical trials with rFVIII-FS in both PTPs and PUPs/MTPs have demonstrated the efficacy (on-demand, prophylaxis and surgery) and safety (viral safety and adverse events) for this preparation. *De novo* inhibitors were not detected in the studies with PTPs (thus no increased immunogenicity associated with the product), and inhibitor incidence was low (15%) over the period of observation for the PUP/MTP study. Formation of antibodies to BHK or murine IgG was infrequent and minor, and when present, not associated with adverse events or interference with efficacy. Postmarketing studies have supported these safety and efficacy results, and additionally, rFVIII-FS has been used effectively for long-term prophylaxis, continuous infusion and ITI.

Expert commentary

Collectively, rFVIII-FS and rFVIII-BHK have now been used for over 17 years, with an excellent record of hemostatic efficacy, low rate of drug-related adverse events, low rate of inhibitor formation, and without a single documented case of viral transmission attributed to either product. While all rFVIII products on the market are safe and effective replacement therapies, differences in cell lines and manufacturing processes differentiate the products. The manufacture of rFVIII-FS differs from its predecessor because it is produced without the addition of albumin during the purification process and final formulation, and solvent/detergent viral inactivation has been incorporated into the process. The low rate of inhibitor formation in PUPs/MTPs treated with rFVIII-FS perhaps distinguishes this product from rFVIII-BHK and other rFVIIIs. However, differences in study design and patient populations complicate comparison of inhibitor rates between studies and products.

Despite the documented benefits of a prophylactic treatment regimen on joint health and quality of life, there are difficulties with compliance [55], and several surveys have helped to provide a better view of the extent to which prophylaxis is used in North America [56–58]. The development of longer-acting FVIII preparations or alternate delivery systems could result in improved adherence to prophylaxis. Modifications of the FVIII protein that may extend the half-life include conjugation of polyethylene glycol (PEG) or polysialic acids to the molecule, or formulation with pegylated liposomes [59]. Preliminary results from prophylactic treatment of severe hemophilia A patients with rFVIII-FS formulated with PEG liposomes showed a significant extension in hemostatic efficacy compared with rFVIII-FS treatment [60]. Safety and pharmacokinetic studies support continued evaluation of the long-term safety and efficacy of this longer acting formulation of rFVIII-FS [61].

As summarized by Lillicrap and colleagues, future approaches to hemophilia (involving treatment of the genetic defects) may take one of several forms: viral gene transfer, cell-based gene therapy, non-viral gene transfer or mutation repair [62].

Until a cure becomes a reality for the global hemophilia community, it is imperative to ensure that safe and effective replacement treatment is available to those who need it.

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Highlights

- Sucrose-formulated recombinant factor VIII (rFVIII-FS; Kogenate® FS) is a native, full length FVIII molecule manufactured from a baby hamster kidney cell line. It is purified and formulated without albumin, and contains sucrose as a stabilizing agent.
- Clinical trials conducted in previously treated patients and previously untreated patients demonstrated the safety (including viral safety and low incidence of inhibitor formation) and hemostatic efficacy of rFVIII-FS. The drug was approved for marketing in the USA and the EU in 2000.
- Postmarketing surveillance studies have supported the initial results from clinical trials for low incidence of inhibitor formation.
- The effectiveness of rFVIII-FS in prophylaxis and on-demand treatment regimens, continuous infusion, and immune tolerance induction has been demonstrated.
- The new reconstitution system associated with rFVIII-FS simplifies reconstitution and provides an additional measure of safety (from exposed needles).

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