Treatment of Haemophilia A with Recombinant Antihaemophilic Factor VIII Products

a report by
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Haemophilia A (classic haemophilia) is an X-chromosome-linked bleeding disorder occurring in approximately one in 5,000–10,000 males worldwide.[1,2] Haemophilia A is caused by a partial or total deficiency of functionally active coagulation factor VIII (FVIII). Haemophilia produces abnormal bleeding that may be mild, moderate or severe depending on the degree of FVIII deficiency. Individuals with severe haemophilia A have FVIII levels <1% of normal activity (<0.01IU/ml), whereas moderate (factor level 0.01–0.05IU/ml) to mild (factor level >0.05–0.40IU/ml) forms have 1–5% and 5–40% of normal activity, respectively.[1] In patients with severe haemophilia A, the first bleeding typically occurs during early childhood. The bleeding can involve any anatomical region but most commonly involves the joints (frequently elbows, knees and ankles) and muscles. Joint haemorrhages can result in severe arthropathy and degenerative damage, as found in osteoarthritis, as well as inflammatory processes similar to rheumatoid arthritis.[3] In contrast to severe haemophilia A, which is characterised by spontaneous bleeding and/or severe bleeding after minor trauma, mild haemophilia A may go undiagnosed until adulthood due to the lack of spontaneous bleeding. The diagnosis of haemophilia A is confirmed by the finding of normal platelet count and function, normal bleeding time, normal prothrombin time and normal von Willebrand factor (VWF). FVIII binding activity is present, but there is prolonged activated partial thromboplastin time (aPTT) and reduced FVIII activity (FVIII:C).[1,2] The diagnosis is completed by molecular genetic testing to identify the genetic defect.

Haemophilia A is incurable, but treatment with antihaemophilic therapy can stop or prevent bleeding episodes, reduce the associated morbidity, improve quality of life and normalise life expectancy. For patients with mild haemophilia A, treatment with desmopressin (DDAVP) is usually sufficient to manage bleeding episodes.[2] However, for patients with mild haemophilia A who do not respond adequately to DDAVP, and for those with moderate or severe forms of the disease, replacement of the deficient factor with commercially prepared FVIII concentrates is generally required. Infusion of these concentrates temporarily increases the plasma level of FVIII and improves clinical symptoms when given on demand for bleeding episodes or during emergency situations or prophylactically to prevent spontaneous bleeding (e.g. in severe haemophilia) or for elective surgery.

Two different types of FVIII concentrates are available for treatment: concentrates purified from donated plasma, with or without VWF, and FVIII products manufactured with recombinant technologies and purified from cell-culture harvest medium. In the past 25 years, advances in the screening of donors and donated plasma, techniques to remove and/or inactivate viruses in concentrates and recombinant technology have remarkably increased the safety and purity of FVIII products. In addition to the full-length FVIII products, a B-domain-deleted (BDD) recombinant FVIII (rFVIII) concentrate that shows clinical haemostatic efficacy in patients with haemophilia A has been developed.[4,5] More recently, an rFVIII product has been developed without the use of human or bovine albumin with the aim of further eliminating the potential risk of viral transmission.[6] In addition to the risk of viral transmission, other product characteristics such as efficacy, tolerability, immunogenicity (development of inhibitors), dosage and administration are also considered when selecting a treatment option for patients with haemophilia A. This article summarises the available evidence for these characteristics of recombinant antihaemophilic factor products for managing haemostasis in patients with moderate/severe haemophilia A.

Recombinant Antihaemophilic Factor Products

Product Specifics

Several recombinant antihaemophilic products – including Recombinate™ (Baxter Healthcare),[7] Kogenate® Bayer (Kogenate® FS; Bayer Healthcare),[8] Helixate®NexGen (Helixate® FS; Bayer Healthcare, distributed by CSL Behring),[9] ReFacto® (Wyeth Pharmaceuticals)[10] and Advate™ (Baxter Healthcare)[11] (see *Tables 1* and *2*) – are commercially available for the treatment of haemophilia A. These are categorised according to their product characteristics, including:

- type of host cell and production details;
- degree of purity;
- viral removal/inactivation processes; and
- presence/absence of animal proteins or human albumin.

Purity and Formulation

There is wide variability among the rFVIII concentrates with respect to final product purity, as reflected by units of specific activity (IU FVIII:C) per milligram of total protein (see *Table 2*). 'Purity' refers to the amount of desired ingredient (FVIII) relative to other protein ingredients (such as albumin as stabiliser). These products contain between 2,000 and 13,000 units of FVIII activity per milligram of protein depending on the type of FVIII molecule (full-length versus BDD), the purification process and whether or not albumin is used as a stabiliser. The currently available rFVIII products are considered very safe as a result of the inclusion (in most of them) of improved virus inactivation and removal steps in the manufacturing process, which minimises the risk of infection from plasma-based additives and DNA technology. The methods currently in use include:

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Table 1: Properties of Recombinant Antihaemophilic Factor VIII Concentrates[6–12]

Property/rFVIII Product	Recombinate™	Kogenate® Bayer/Helixate®NexGen	ReFacto®	Advate™
Generation	First	Second	Second	Third
FVIII molecule	Full-length	Full-length	B-domain-deleted	Full-length
Cell line	CHO	BHK	CHO	CHO
FVIII stabiliser	Human albumin	Sucrose	Sucrose	Trehalose
Animal/human plasma proteins in cell medium	Yes (bovine)	Yes (human)	Yes (human)	No
Animal/human plasma proteins in purification and final formulation	Yes (human)	No	No	No

BHK = baby hamster kidney; CHO = Chinese hamster ovary; FVIII = factor VIII; rFVIII = recombinant factor VIII.

Table 2: Characteristics of Recombinant Antihaemophilic Factor VIII Concentrates[6–12]

Characteristic	Recombinate™	Kogenate®Bayer/Helixate®NexGen	ReFacto®	Advate™
Indication	Haemophilia A • peri-operative management of haemostasis	Haemophilia A with deficiency of FVIII	Haemophilia A prevention/ control haemostasis • surgical prophylaxis • short-term routine prophylaxis	Haemophilia A • peri-operative management of haemostasis
Technology	Recombinant	Recombinant	Recombinant	Plasma/albumin-free recombinant
Purity	>4,000IU/mg protein (much less including albumin)	>4,000IU/mg protein	Up to 13,000IU/mg protein	>4,000IU/mg protein
Viral removal method	• 2 x ion-exchange chromatography • Immunoaffinity chromatography on MAbs	• 3 x ion-exchange chromatography • Gel filtration • Immunoaffinity chromatography on MAbs	• 2 x ion-exchange chromatography • Immunoaffinity chromatography on MAbs • three other chromatographies	• Immunoaffinity chromatography on MAbs • 2 x ion-exchange chromatography
Viral inactivation method	No specific method	Solvent/detergent	Solvent/detergent	Solvent/detergent
Half-life	14.6±4.9 hours	13 hours	14.8±5.6 hours	11.98±4.3 hours
In vivo recovery	2.4% IU/dl/IU/kg	2.1±0.3% IU/kg	2.4±0.4% IU/dL/IU/kg	2.4% IU/dl/IU/kg
Diluent volume	10ml sterile water • 250IU • 500IU • 1,000IU	2.5ml sterile water • 250IU • 500IU • 1,000IU	4ml sodium chloride • 250IU • 500IU • 1,000IU • 2,000IU	5ml sterile water • 250IU • 500IU • 1,000IU • 1,500IU

MAbs = monoclonal antibodies.

- Virus inactivation:
  - chemical (solvent/detergent) procedures.
- Virus elimination:
  - different types of conventional chromatographies;
  - ultrafiltration methods; and
  - immunoaffinity chromatography: separation with monoclonal antibodies.

The current products are described as three generations of rFVIII, which differ primarily in the use of animal and/or human plasma proteins in the cell medium and final formulation (see *Table 1*).[6,7–12] The first-generation products contain animal proteins in the cell medium and use human albumin during purification and in the final formulation (as a stabiliser). The second-generation products contain an improved formulation that substitutes albumin for sucrose in the purification and final formulation. The third-generation product even eliminates animal and human plasma proteins in the cell culture medium.

Efficacy

It is not possible to make direct comparisons of haemostatic efficacy between the different antihaemophilic rFVIII products due to the lack of comparative clinical trials. There is only one published study that has directly compared the pharmacokinetics of Advate with those of ReFacto.[13] This study did not observe any significant differences between the two products. Data from pivotal trial programmes and post-marketing surveillance studies additionally support the impression that the currently available rFVIII products are equally effective and similar to the established plasma-derived (pd) products in preventing and controlling bleeding episodes in patients with haemophilia A (primarily in those with moderate or severe disease). In most cases, one or two single bolus infusions of the antihaemophilic factor concentrate result in efficacy ratings of 'excellent/good' in over 85% of patients, including paediatric[14] and adult patients, previously untreated patients (PUPs),[5,15–17] minimally treated patients (MTPs)[16,18] and previously treated patients (PTPs).[5,19–23] The case is the same for those undergoing surgical or invasive procedures,[23–26] those receiving prophylaxis[17,27] and those in long-term and home treatment settings.[19,28,29] Furthermore, continuous infusion therapy with some rFVIII products has demonstrated efficacy ratings of 'excellent/good' in the majority of haemophilia A patients.[19,30–32] More recently, prophylactic infusions of rFVIII have demonstrated significant reductions in the incidence of not only bleeding episodes but also joint haemorrhages and the associated joint damage of young children with severe haemophilia A.[33]

Safety

Adverse Events

Since the development of the first rFVIII product in 1992, all rFVIII products have been assessed extensively regarding their safety and tolerability profiles. Adverse events, which are similar among the rFVIII products, are generally infrequent and mild in nature and include headache, nausea, dizziness, fever, lethargy and altered taste.[7–11] Allergic reactions are rare for all products. In pivotal trial programmes and post-marketing surveillance studies, the majority of physicians and/or patients

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Table 3: Factors Affecting the Occurrence of Factor VIII Inhibitors in Patients with Haemophilia A[35,37,40–42]

Factor	Occurrence of Inhibitors
Type of haemophilia	More common in patients with severe haemophilia than in those with either mild or moderate forms of the disease.
Mutation type and severity	Occur in 30–40% of patients with mutations that prevent the formation of FVIII such as: • gene deletions; • non-sense mutations causing premature stop codons; and • FVIII gene inversions.
Family history	More common in those with a family history of inhibitors.
Ethnicity	More common in Africans than Caucasians.
Other	May be affected by: • intensity of first treatment; • mode of treatment (prophylaxis versus on-demand); • age at first treatment; • type of haemorrhage; • type of FVIII concentrate (pd-FVIII versus rFVIII); • switching FVIII products; and • length of treatment.

Table 4: Occurrence of Inhibitors to Factor VIII with Recombinant Factor VIII Concentrates in Patients with Haemophilia A[5,7–11,22,50]

Patient	Recombinate™	Kogenate®Bayer/ Helixate®NexGen	ReFacto®	Advate™
PTPs	2.9%	<2%	2.8%	0.9%
PUPs	30%	15%	32%	NA*

NA = data currently not available as clinical trial in PUPs is still ongoing.*
PTPs = previously treated patients; PUPs = previously untreated patients.

considered the safety and tolerability of rFVIII products to be 'very good/good'.[5,17] Nowadays, the most serious side effect of treatment with FVIII products is the formation of inhibitors (alloantibodies), because they neutralise the activity of the clotting factor and make the management of bleeding episodes difficult, with the potential for uncontrollable bleeding and increased morbidity and mortality.

Risk of Immunogenicity

The development of inhibitor antibodies against FVIII is a common and severe treatment complication of haemophilia A.[34–37] Inhibitors occur in up to 33% of patients with severe haemophilia A, usually within the first 50 days of exposure.[38] These inhibitors have primarily been observed in previously untreated children, and around 30% disappear on continued treatment with the same product.[39] The formation of inhibitors depends on the many factors that are outlined in *Table 3*. Of particular interest is the influence of the type of replacement concentrates on the risk of inhibitor formation, and whether switching between FVIII products increases this risk. The occurrence of inhibitor formation with FVIII concentrates has been compared in different studies among various products. While a few studies such as the Concerted Action on Neutralizing Antibodies in Severe Haemophilia A (CANAL) trial indicate that the rFVIII products have a similar propensity to elicit FVIII inhibitors,[43] some other studies suggest that rFVIII products are more immunogenic than pd-FVIII concentrates.[35,41] However, most of these studies used first-generation rFVIII products that are different from the current ones in many respects. For example, recent experimental findings suggest that differences in the purity of the products and the presence of VWF may reduce the immunogenicity of FVIII.[44,45]

Switching from one concentrate to another could potentially expose a patient to neoantigens, and thereby increase the risk of inhibitor formation.[12] However, current evidence on inhibitor occurrence when switching either from a pd-FVIII to an rFVIII concentrate or between rFVIII products remains controversial, and clearly requires longer-term prospective follow-up.[17,43,46–49] However, the European Medicines Agency (EMEA) has introduced a class warning for all rFVIII products stating that: "Cases of recurrence of inhibitors (low-titre) have been observed after switching from one recombinant factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development".[50] Among the various commercially available rFVIII products, non-comparative trial data indicate that the incidence of inhibitors ranges from 15% with Kogenate Bayer/Helixate NexGen to as high as 32% with ReFacto in PUPs; and in PTPs, the incidence ranges from 0.9% with Advate to 2.9% with Recombinate (see *Table 4*).[5,15,19,51–53] These incidences are in most cases higher than those observed with pd-FVIII concentrates.

Risk of Viral Transmission

The risk of transmission of blood-borne viruses, including human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV) viruses, as well as bacteria and protozoans by contaminated plasma products, has virtually been eliminated by introducing comprehensive safety measurements.[12] In addition, in all but one of the currently marketed rFVIII products, a solvent/detergent inactivation step was introduced to inactivate enveloped viruses that theoretically might be in the harvest medium as a contaminant from the cell culture or from the plasma additives. Nevertheless, the third-generation rFVIII product was developed to offer the additional advantage of being manufactured in an albumin- and plasma-free medium, which is thought to even further reduce the risk of transmitting blood-borne pathogens. All of these measures guarantee a very high level of pathogen safety for the rFVIII products.

Dosage and Administration

Dosing regimens for FVIII concentrates in haemophilia are generally based on *in vivo* recovery (IVR) and biological half-life. IVR is the ratio of the observed peak factor concentration to the predicted peak factor concentration, and can vary depending on the patient's plasma volume and dose of factor. The currently available rFVIII products result in a rise of at least 2% per IU/kg of infused factor (see *Table 1*). The published product half-lives range from almost 12 hours with Advate to almost 15 hours with ReFacto. The diluent volumes range from 2.5ml (Kogenate Bayer/Helixate NexGen) to 10ml (Recombinate) per vial, with some vials containing different potencies of product. The smaller the diluent volume, the more convenient the administration, due to less time needed for infusion of the highly concentrated products. The dose and duration of therapy with rFVIII concentrates depends on the site, size and severity of the bleeding episode, presence of inhibitors, previous anamnestic response, desired FVIII level and the individual needs of the patient. Replacement factor products are administered as intravenous bolus infusions for the majority of bleeding episodes. However, for surgical prophylaxis, continuous infusion of FVIII concentrates may be the preferred treatment approach. Continuous infusion regimens offer the potential for cost and product savings owing to better steady-state pharmacokinetics, the need for less product and a more convenient and simplified treatment option by eliminating the need for frequent bolus injections and blood sampling.[32] Kogenate Bayer/HelixateNexGen is the only rFVIII product that has received European approval for use as a continuous infusion for patients with haemophilia undergoing major surgery.

Choice of Recombinant Factor VIII Product

Recombinant FVIII products have become accepted alternatives to the established plasma-derived concentrates for the treatment of haemophilia A and thereby continue the trend of the last 20 years towards higher purity and specificity. All of the commercially available recombinant antihaemophilic factor products demonstrate similar 'excellent/good' haemostatic efficacy and similar tolerability in patients with moderate or severe haemophilia. The safety profiles of these products are also similar, although one of the products has no virus inactivation implemented and the overall reported risks of inhibitor formation in PUPs is different and by far the lowest with Kogenate Bayer/HelixateNexGen, but similar between all products in PTPs. Dose and administration are also considerations for selecting a treatment option; features such as vial/diluent size, ease/convenience of administration, intensity of treatment (such as continuous infusions) and reconstitution/delivery system all contribute to the final decision. Other factors that influence treatment choices include cost, availability and patient/physician preference. ■

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