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COMMEMORATIVE ARTICLE

Development and introduction of recombinant factor VIII – a clinician's experience

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In this review concerning the state of treatment for persons with haemophilia A leading up to the development and introduction of recombinant factor VIII products, and beyond, I vividly recall my own feelings at the time. When I began my fellowship training in paediatric haematology in the mid-1960s, we almost always had numerous boys in the hospital, receiving large volumes of fresh frozen plasma every 6–8 h for joint or large soft tissue haemorrhages. If they developed an inhibitor, there was little that we could do. A short time later, we were able to obtain cryoprecipitates, and then, by 1970, intermediate purity, lyophilized FVIII concentrates. These seemed wonderful, allowing out-patient treatment, and even surgical procedures! However, it soon became apparent that there was a price to be paid for the use of these plasma-derived products as most of our patients developed hepatitis, and by the early 1980s, AIDS. As a result, there were attempts to make the lyophilized, plasma-derived FVIII concentrates safer (improved donor screening, dry heat treatment, solvent-detergent treatment, pasteurization); however, by 1987, when recombinant FVIII concentrates became available for prelicensure clinical trials, there was genuine excitement! Excitement by me and most of my colleagues throughout the U.S. and abroad, and also a great deal of excitement by our patients, many of whom had affected family members or friends who had developed the acquired immunodeficiency syndrome (AIDS).

In the 1950s and much of the 1960s, bleeding episodes in persons with haemophilia were treated with fresh frozen plasma (FFP), as no one had come up with a method for separating F VIII or F IX from plasma. Patients with bleeding episodes were frequently hospitalized for infusions of large volumes of FFP given every 6–8 h in an attempt to stop bleeding without pushing them into congestive heart failure from fluid overload. A major breakthrough came in 1965, when Dr. Judith Poole described a simple way of separating FVIII (and vWF) from plasma which had been frozen and then thawed in the cold [1]. Almost overnight, cryoprecipitates (cold insoluble precipitates) were being produced by blood collection facilities, for treatment of persons with haemophilia A. These cryoprecipitates had to be stored in the frozen state prior to use, and varied in the amount of FVIII contained. A short time later, two pharmaceutical companies had developed technologies to separate FVIII (and FIX) from large pools of donor plasma, resulting in freeze-dried, lyophilized FVIII concentrates [2]. These early, intermediate purity FVIII concentrates were easier to use, as they did not need to be frozen for storage, and each bottle was labelled with the amount of FVIII contained. However, neither cryoprecipitates or these intermediate purity plasma-derived concentrates were treated for blood-borne viruses. Once these lyophilized concentrates became available, treatment for bleeding episodes was much easier, haemostatic levels of FVIII could easily be achieved and, in the early 1970s, home treatment programs sprung up. The latter resulted in earlier treatment of joint bleeds, and a greater feeling of independence for those with haemophilia. Many referred to this period as the 'golden age' for haemophilia. However, this feeling was short-lived, as in 1981 the Communicable Disease Center (CDC) described the first three persons with haemophilia A who developed the acquired immunodeficiency syndrome (AIDS), and these three were followed by more and more individuals with haemophilia, many of whom died of its complications [3–5]. In addition, it had become increasingly apparent that many persons with haemophilia had been infected with hepatitis viruses [5] (hepatitis B and so-called, 'non-A, non-B' hepatitis, subsequently called hepatitis C after the HCV was identified).

These serious complications of treatment resulted in increased efforts to make treatment safer. Lyophilized, intermediate purity concentrates were treated with dry heat [5]. Cryoprecipitates were no longer recommended for treatment of haemophilia A, being considered less safe than heat-treated products [6]. In 1981 Haemate P, a pasteurized FVIII and vWF concentrate became available in Germany. Predominantly used in Europe, this product was the first effectively virus-inactivated FVIII product [7]. Shortly thereafter, other products of

higher purity were developed, using monoclonal antibodies to FVIII or von Willebrand Factor (vWF) [8–11]. The production of these higher purity concentrates included multiple purification and virucidal steps (including heat treatment, solvent detergent treatment) to reduce the risk of viral transmission. However, during the relatively short-term hepatitis safety trials with these high purity FVIII concentrates, inhibitor assays (which were done at baseline and again at 6 months) demonstrated that some of the previously untreated subjects (PUPs) developed inhibitors to FVIII [8,9]. This was alarming at the time, and subsequently all prospective clinical trials in haemophilia A patients incorporated more frequent inhibitor assays and a longer duration of follow-up.

In view of the high rate of transmission of blood-borne viruses by plasma-derived concentrates in the 1970s and early 1980s, there was a great deal of interest in the possibility of producing 'synthetic' FVIII and FIX. This possibility became reality for FVIII in 1984 by the successful determination of structure, and cloning and expression of the Factor VIII gene by scientists at the Genetics Institute (in Cambridge, MA) and Genentech (Berkeley, CA). The prospect of viral safety associated with FVIII produced from recombinant DNA technology was the main advantage, but additionally, rFVIII could – at least theoretically – become available in unlimited supply.

These accomplishments, published in a single issue of 'Nature' in 1984 [12–15], were remarkable in view of the size and complexity of the FVIII gene which encompassed 186,000 base pairs and represented 0.1% of the human X chromosome. In a very short time thereafter, in collaboration with scientists at Genentech and the Genetics Institute, two U.S. Pharmaceutical Companies (Miles, Inc./Cutter Biological, Berkeley, CA, and Baxter/Hyland Div., Glendale, CA) accomplished scale-up, purification and standardization of two rFVIII products for clinical use.

Following preclinical in vitro studies, and studies in animals, prelicensure clinical trials in patients with haemophilia A began in 1987 [16]. Safety and efficacy in treatment of bleeding episodes and in controlling bleeding in major surgery was documented in adults [17,18]. Recombinate was licensed for use in the U.S. in 1992 and Kogenate was licensed for use in early 1993. In January 1989, a study in previously untreated patients (PUPs) was begun with Kogenate [19], and in July, 1990, the PUP study with Recombinate began [20,21]. Clinicians involved in these early trials with rFVIII products found that it was relatively easy to enrol subjects, all of whom had heard about AIDS and hepatitis with plasma-derived products. In both of the PUP trials, haemostatic responses were excellent and the products were well tolerated. However, inhibitor antibodies developed early (after a median of 9–11 EDs) in 20–25% of study subjects. Approximately half of the inhibitors in both PUP studies were 'high responding' (>5 BU), whereas the remainder were 'low responding' and most of these were transient [22–24]. Nevertheless, some clinicians became concerned that recombinant FVIII was causing a higher incidence of inhibitors.

However, earlier studies in infants and children with severe haemophilia A published in 1992 and 1993 had documented a higher incidence of inhibitor development with plasma-derived FVIII (25–50%) [25,26] than previously thought. It had become increasingly apparent that, if one looks for inhibitors prospectively, with laboratory monitoring at frequent intervals, 25–35% (or even 50%) of PUPs will develop inhibitors after a median of 9–11 EDs. Roughly one-third of these will disappear despite continued exposure to FVIII given for episodic treatment. In addition, it was becoming increasingly apparent that such findings were not related to a particular type of product, but were seen with plasma-derived as well as rFVIII products [27]. Other analyses were documenting that patient-related factors, such as the severity of haemophilia, FVIII gene mutation causing the person's haemophilia, race, etc., were more important determinants of inhibitor development [27].

It had also become apparent that very few persons with severe haemophilia who had received >50 EDs with plasma-derived FVIII, developed de novo inhibitors while on rFVIII. These findings led to the 1999 recommendation by the Scientific Subcommittee on Factor VIII and Factor IX of the ISTH's Scientific and Standardization Committee that only previously (and heavily) treated haemophilia patients would be used for determining the immunogenicity of any new FVIII product [28].

Although the benefits of rFVIII products appeared to be enormous (increased viral safety, greater peace of mind), there was still some concern over the fact that the original rFVIII products, Kogenate and Recombinate, contained pasteurized human serum albumin (HSA) as a stabilizer. Pasteurized HSA had an excellent safety records, and there was no indication that it caused any problems in recipients. Nevertheless, HSA was later replaced with sucrose as a stabilizer (e.g.: Kogenate FS, which is formulated with sucrose) [29–32].

As newer, so-called 'second generation' rFVIII products were developed, some clinicians worried that these might be more immunogenic. Pharmacia's (Stockholm, Sweden) B-domainless rFVIII (rFVIII SQ) [33,34] entered prelicensure clinical trials in 1993 in Europe, and in the U.S. in 1995. No albumin is needed to stabilize B-domainless rFVIII; however, it was used in the manufacture of the product. B-domainless (BDD) rFVIII (ReFacto, now referred to as Xyntha, Wyeth Pharmaceuticals, Collegeville, PA), has not been associated with an increased incidence or prevalence of FVIII inhibitors as compared with plasma-derived or full-length rFVIII products in PTPs or PUPs [35–39].

From the introduction of the first rFVIII concentrates in the late 1980s, through each new variation, there have been carefully designed, long-term, prospective clinical trials in both PTPs and PUPs to look at safety and efficacy. These have included frequent inhibitor assays, as well as other laboratory and clinical observations. Each of these rFVIII preparations have proven to be safe and effective. None have resulted in an increased incidence or prevalence of inhibitors [40]. On the other hand, a large body of useful information has been gained from these (and other) studies which have improved our understanding as to which patients are at greater risk of developing an inhibitor, what are the important genetic and environmental risk factors; long-term viral safety of FVIII products, etc.

So, while there was some concern – particularly about the possibility of increased immunogenicity – with the introduction of rFVIII concentrates in 1987, and there has still been concern with the introduction of each new rFVIII methodology (now with longer acting rFVIII preparations), to date, the benefits for patients have far outweighed any of our worries about risks – especially in view of the rigours of each prelicensure study designs, and pharmacovigilance on the part of manufacturers.

Disclosures

The author stated that she had no interests which might be perceived as posing a conflict or bias.

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