

## The Evolution of Hemophilia A Therapy

Transfusion therapy for hemophilia was first proposed in the mid-19th century, and whole blood transfusion began early in the 20th century.<sup>1</sup> The evolution of plasma replacement therapy had a tremendous impact on management of hemophilia. The large volumes of blood or citrated plasma replacement required to achieve hemostasis following major bleeding episodes evolved over time,<sup>2</sup> first to more manageable amounts of cryoprecipitate,<sup>3</sup> and then to highly purified plasma-derived FVIII (pdFVIII) concentrates.<sup>4</sup>

These concentrates produced reliable hemostatic efficacy but production of the volumes needed required the use of large plasma pools. This, in turn, gave rise to serious issues of blood-borne pathogen transmission.<sup>5,6</sup> This unfortunate extreme manifestations of transfusion-transmitted diseases, such as human immunodeficiency virus (HIV), hepatitis B, and hepatitis C shifted the focuses on the technologic advances that resulted in even more "pure" replacement therapies for safety w.r.t., blood-borne pathogen transmission and FVIII inhibitor development.

Thus for improved diagnostic and procedural antiviral measures became essential.<sup>7</sup> Donor selection has now become rigorous and advanced assays for screening donated plasma have been introduced. Alongside these efforts to prevent contamination of the plasma pool, viral inactivation and elimination techniques have been further developed.<sup>7,8</sup>

Baxter has played a leading role in these developments. HEMOFIL-T, a plasma-derived heat treated concentrate of human factor VIII (FVIII), was initially developed by Baxter to lower the specific risks for transmission of HIV, HBV and HCV. Shortly thereafter, Baxter further improved the safety of treatment for hemophilia with HEMOFIL-M, the first monoclonally purified pdFVIII that was subjected to a solvent/detergent viral inactivation process. In 1992 Baxter made another major advance in the safety of FVIII replacement therapy with the development of the first commercially available recombinant FVIII concentrate.

As recombinant FVIII concentrates are not dependent on pools of human plasma as a source of FVIII protein, their introduction has substantially lowered the risk for pathogen transmission historically associated with plasma-based hemophilia therapies.<sup>7,8</sup> The development of rFVIII concentrates was a major accomplishment in biotechnology that required the cloning and introduction of the FVIII gene into suitable host cell lines, and subsequent characterization of the expressed proteins. An equally remarkable feat of manufacturing expertise was required to

achieve purification, formulation, and validation of a finished rFVIII therapeutic on a commercial scale.<sup>7</sup>

## **Hemophilia therapy in India**

It is estimated that in India, with population more than 1000 million, there should be at least over 100,000 hemophilia A patients in the country and at least 50,000 persons with severe hemophilia.<sup>9</sup> Of these, less than 15% of estimated number have been diagnosed.<sup>9,10</sup> The data available with Hemophilia Federation of India gives the number of people with hemophilia who receive treatment as 12,500<sup>11</sup>

Access to factor concentrates is not uniform throughout the country and depends not only on the socio-economical factors but also on local availability. The cryoprecipitates and fresh frozen plasma are still being used in the treatment of hemophilia in spite of their inherent drawbacks like need for fresh blood, need to infuse large quantities to stop bleeding and above all the risk of transmission of viral infections like HIV, HBV, HCV and etc. Very few of the identified patients receive Factor VIII replacement treatment. Also, in Indian hemophiliacs, the factor concentrates have been used in negligible amounts, often to stop unstoppable blood loss and in extremely painful muscle and joint haematomas or in life threatening cerebral and GI bleeds.<sup>11</sup> In India, hemophilia is treated with minimal replacement therapy of about 2000 IU/PWH/Year as opposed to 11,000 IU/PWH/Year in Malaysia and 12,000 IU/PWH/Year in South Africa in their Public Hospitals.<sup>12</sup>

The pathogen safety issue has taken its toll in India. About 10-14% of PWH in India have hepatitis B infection and 24-30% of them are positive for hepatitis C.<sup>13</sup> Because of regulations imposed by the Government of India and help given by National AIDS Control Programme the prevalence of HIV-1 infection among haemophilics has reduced from 13-14 to 6% at present.<sup>13</sup> These viral transmissions are unlikely to reduce without universal use of high purity factor concentrates or recombinant products for haemophilia care.

## References:

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