Recombinant FVIII: the milestone of modern hemophilia treatment

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TITLE	Use of recombinant antihemophilic factor in the treatment of two patients with classic hemophilia.
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On January 19, 1989, the Medical Intelligence section of the New England Journal of Medicine reported the first use of recombinant factor VIII (FVIII) in two patients with severe hemophilia A (HA).[1] This article represents a landmark in its field because it marks two distinct periods of hemophilia care. The first started in the 1970s, when the availability of FVIII concentrates manufactured from human plasma offered the first efficacious form of replacement therapy in bleeding disorders. However, this success story of the 1970s was followed by the mayhem of the 1980s, when many patients with hemophilia developed the acquired immune deficiency syndrome (AIDS) that had been transmitted by concentrates manufactured from pooled human plasma, leading to a dramatic death toll. The scientific research community reacted promptly with the identification of human immunodeficiency virus (HIV) as the cause of AIDS, the development of diagnostic methods, and the demonstration of the efficacy of heating to inactivate HIV in plasma-derived concentrates and so to ensure once again safety.

Another strategy that was pursued was to tackle the problem of bloodborne infections by means of DNA technologies that, at that time, were developing at a fast pace. In this framework, it was a monument to ingenuity that, in November 1984, Nature published four articles in the same issue, authored by scientists from such biotechnology giants as Genentech and Genetics Institute, on the cloning of the huge FVIII gene, and the structure and se-

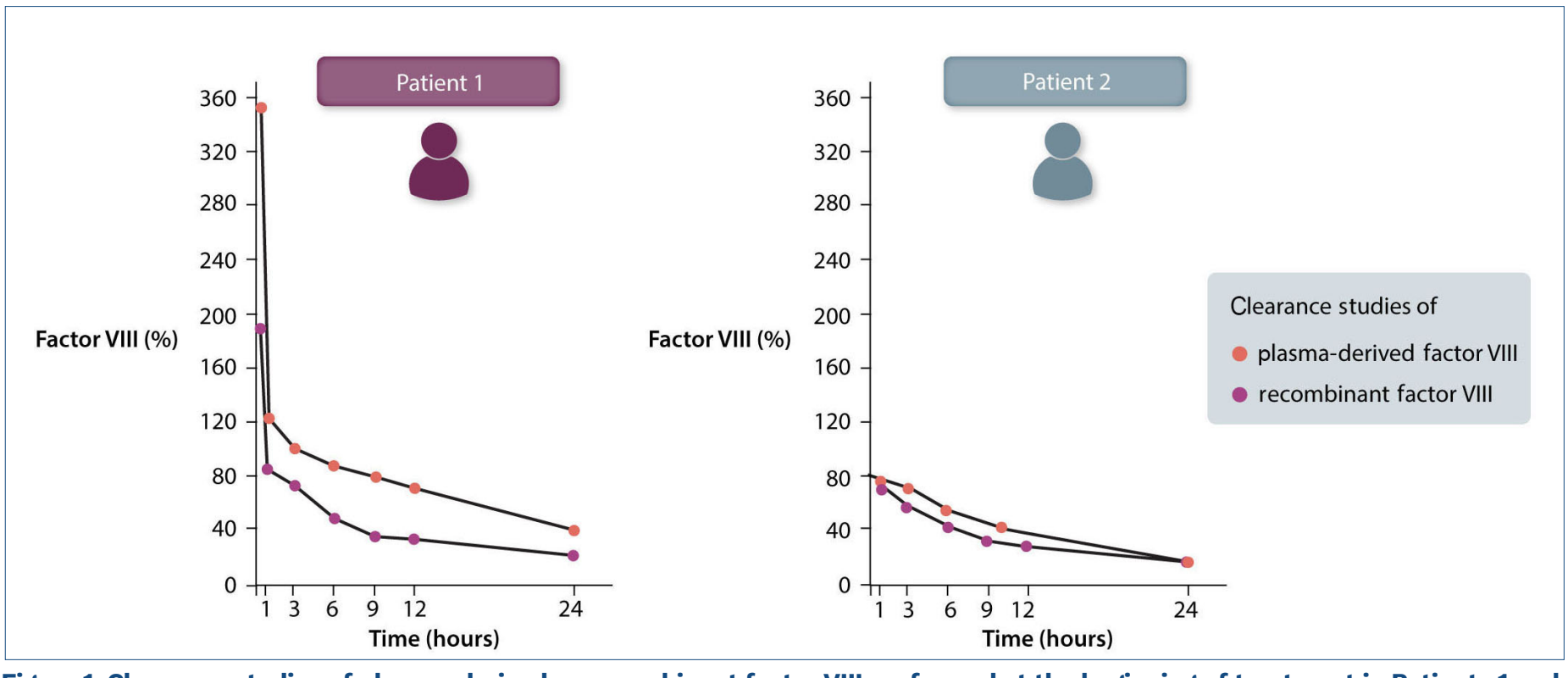

Figure 1. Clearance studies of plasma-derived or recombinant factor VIII performed at the beginning of treatment in Patients 1 and 2. Figure adapted with permission from White *et al.* N Engl J Med 1989.

quence of this complex and labile coagulation factor. John Maddox, the editor of Nature, applauded FVIII gene cloning as "a technical triumph without parallel",[2] considering that, at the time, only such relatively simple molecules as insulin and human growth hormone were being manufactured for clinical use by recombinant DNA technology. It took a few more years to bring recombinant FVIII to the bedside. The two pioneer biotechnology companies partnered with pharmaceutical companies involved in hemophilia care for the large-scale manufacturing of recombinant FVIII: Genentech with Bayer, Genetics Institute with Baxter Healthcare. The fiercely competitive race to the first clinical use of recombinant FVIII was won by Genetics Institute and Baxter, who were able to supply White *et al.*[1] with enough product to safely and successfully treat bleeding in two patients with severe HA and HIV positivity (Figure 1). The Baxter product was authorized for sale by the US Food and Drug Administration with the proprietary name of Recombinate® in December 1992, and Bayer Kogenate® in early 1993.

These products, and others that subsequently became available in the 1990s, represent a pivotal moment in hemophilia care, and mark a substantial shift in the therapeutic approach: from the use of replacement therapy only in the event of bleeding episodes or before invasive procedures, to prevention by means of the continuous administration of FVIII, a regimen that, until then, had been unrealistic because of the perceived poor safety and limited availability of plasmatic products.

The wider implementation of prophylaxis in the 1990s reached a climax in 2007, when the publication of a randomized clinical trial[3] provided concrete evidence that this treatment regimen was superior to episodic treatment of bleeding, a huge achievement in such a rare disease as hemophilia. These advances, and the amazing further progress that has materialized over the last ten years,[4] have offered people with hemophilia, at least in high-income countries, a life expectancy similar to that of the general male population.[4]

Disclosure

No conflicts of interest to disclose.

References

1. White GC 2nd, McMillan CW, Kingdon HS, Shoemaker CB. Use of recombinant antihemophilic factor in the treatment of two patients with classic hemophilia. N Engl J Med. 1989;320(3):166-170.
2. Maddox J. Who will clone a chromosome? Nature. 1984;312(5992):306.
3. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007;357(6):535-544
4. Mannucci PM. Hemophilia treatment innovation: fifty years of progress and more to come. J Thromb Haemost. In press.