Growing weapons to fight hemophilia

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Very few rare diseases have witnessed the gigantic progress in patient care that took place for the hemophilias in the last 20 years. The first landmark was in the 1990s, when recombinant DNA technology afforded the industrial production, regulatory approval and commercialization of an array of factor VIII (FVIII) and factor IX (FIX) products,[1] potentially available in unlimited quantity, efficacious and free from the risk of transmission of such bloodborne infections as HIV and the hepatitis virus B and C (Figure 1). Recombinant FVIII made feasible one of the few randomized clinical trials ever done in such a rare disease as hemophilia.[2] Its results provided for the first-time unequivocal evidence that prophylactic replacement therapy was superior to the episodic management of bleeding episodes for the prevention of arthropathy, the main chronic consequence of hemophilia. Following this trial and the availability of recombinant products prophylaxis, pioneered in Sweden,[3] but not implemented on a large scale elsewhere, became truly feasible.

The snag of prophylaxis was the need to administer recombinant FVIII by intravenous injections that, owing to the short plasma half-life of this protein, had to be generally carried out at alternate days in order to transform severe hemophilia A (plasma levels FVIII less than 1%) into a moderately severe disease (factor levels of at least 2-3%) and, thereby, minimize the rate of bleeding episodes.[4] To give an idea of the burden of prophylaxis, the average patient with severe FVIII deficiency had to undergo as many as 160-180 yearly venipunctures, with inevitable adherence issues particularly for children and patients with an active lifestyle. As much as recombinant DNA technology was the turning point in the 1990s to start effective patient care, this technology was again employed in the 2010-2020 decade in the attempt to extend the relatively short plasma half-life of coagulation factors, increase the time interval between the doses and ultimately reduce the number of venipunctures. Two main protein modification techniques have been employed to obtain therapeutic factor products with a more extended half-life: recombinant fusion with plasma proteins endowed with a long half-life such as albumin and the Fc component of IgG1 immunoglobin or conjugation with a chemical such as polyethylene glycol (PEG). Both these techniques have been implemented by industrial manufactures of recombinant FVIII and FIX products, so that at the time being 7 different brands are approved by the regulatory agencies Food and Drug Administration in the USA and European Medicines Agency in Europe (Table 1).[5,6] The pivotal clinical trials that led to the approval and commercial availability of these products showed that both the protein modification techniques were able to extend the plasma half-life of the coagulation factors deficient in the hemophilias: in average from 12-14 hours to 16-18 for FVIII, more so for FIX (from 18-22 to 90-100 hours) (Table 1).[5,6]

The clinical advantages in terms of reduction of the yearly number of intravenous injections are unequivocal: from 180 to 120 injections for hemophilia A, from 100 to 50 for hemophilia B. The definite but only partially satisfactory extension of the half-life of FVIII products led to

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Citation: Mannucci PM. Growing weapons to fight hemophilia. Bleeding, Thrombosis, and Vascular Biology 2023;2:64.

Key words: hemophilia, recombinant prophylactic therapy, rFVIII plasma half-life, efanesoctocog

Conflict of interest: The Author declares no potential conflict of interest.

Funding: None.

Received for publication: 16 February 2023.
Accepted for publication: 17 February 2023.

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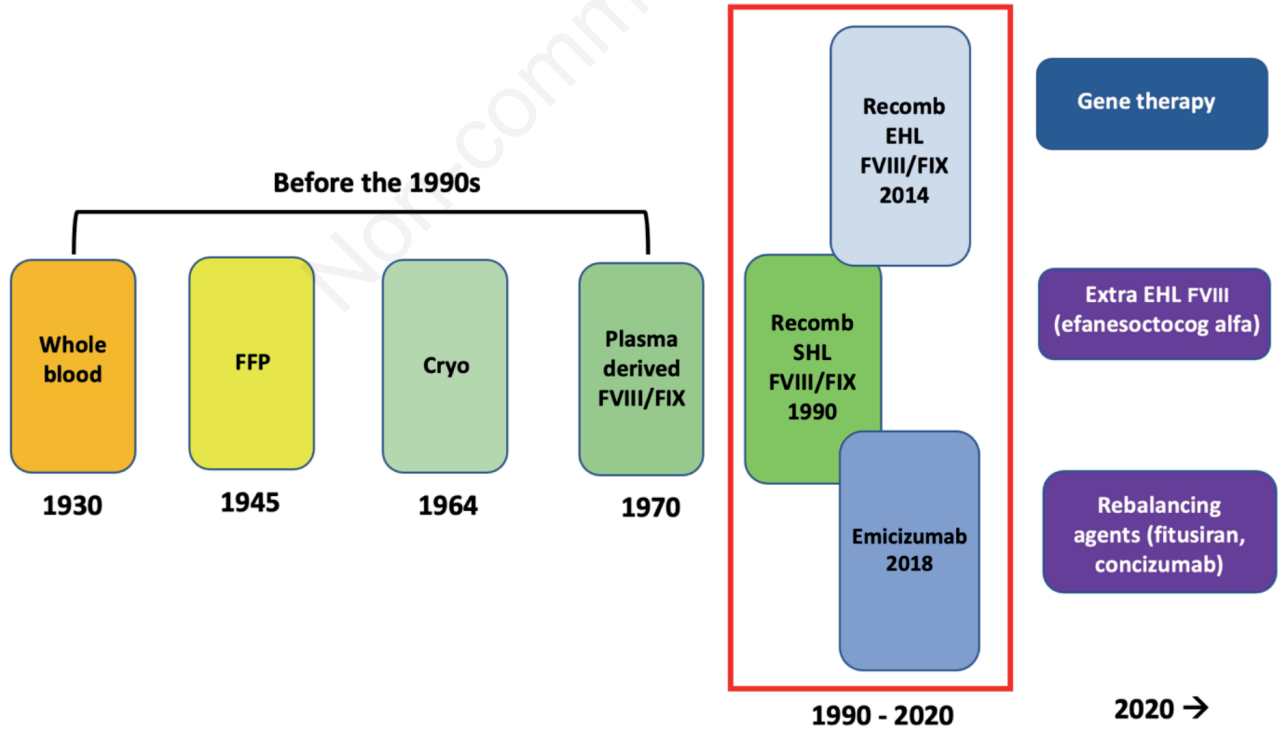
Bleeding, Thrombosis and Vascular Biology 2023; 2:64
doi:10.4081/btvb.2023.64

further research efforts and to the novel medicine efanesoctocog alfa.[7] However, a preamble is needed to explain why the extension of FVIII plasma half-life was less than satisfactory at variance with that of FIX. The point of the matter is that whereas FIX circulates free in blood, FVIII binds to another plasma protein, von Willebrand factor (VWF), and thus acquires the half-life of its chaperon, only slight longer than that of FVIII (16-18 hours). Hence, binding of VWF creates a ceiling to the efforts to prolong FVIII half-life, because the FVIII products modified by protein fusion or PEG conjugation bind to VWF in plasma and thus depend on the half-life of the latter protein. Efanesoctocog alfa is a monument of ingenuity in terms of molecular engineering.[7] To each FVIII molecule the manufactures were able to attach by fusion 1 Fc molecule and 2 synthetic polypeptides XTEN.[7] However, the truly crucial step was the addition to

Table 1. Factor VIII and IX recombinant products with extended plasma half-life.

Protein name and approval year	Brand name and manufacturer	Protein modification technology	Plasma half-life (hours)	Time longer half-life
Efmoroctocog alfa, rFVIII (2014)	Elocta/Eloctate, Sobi	Fc-fusion	19	1.5-1.7
Eftrenonacog alfa, rFIX (2014)	Alprolix, Sobi	Fc-fusion	82	4.3
Rurioctocog alfa pegol, rFVIII (2015)	Adynovi/Adynovate, Baxalta/Takeda	PEGylatedb (2x20 kDa)	14.3	1.3-1.5
Albutrepenanocog alfa, rFIX (2016)	Idelvion, CSL Behring	Albumin-fusion	101	5.3
Nanocog beta pegol, rFIX (2017)	Refixia, Novo Nordisk	GlycoPEGylatedb (40 kDa)	93	5.8
Damoctocog alfa pegol, rFVIII (2018)	Jivi, Bayer	PEGylatedb (60 kDa)	19	1.6
Turoctocog alfa pegol, rFVIII (2018)	Esperoct, Novo Nordisk	GlycoPEGylatedb (40 kDa)	18.4	1.6
Efanesoctocog alfa, rFVIII, not yet approved	Sanofi/Sobi	FC fusion, XTEN polypeptide fusion, VWF D'D3 fusion	43.3	3-4

rFVIII, recombinant factor VIII; rFIX, recombinant factor IX; FC, fragment crystallizable; PEG, polyethylene glycol.



FFP, fresh frozen plasma; Cryo, cryoprecipitate; FVIII, factor VIII; FIX, factor IX; SHL, standard half-life; EHL, extended half-life.

Figure 1. Therapeutic advances in hemophilia.

FVIII by molecular engineering of the D'D3 domain of recombinant VWF, the site where FVIII binds to its chaperon.[7] This intriguing and seemingly paradoxical step succeeded in disconnecting the half-life of FVIII from that of VWF and thus to counter the half-life ceiling due to the binding of FVIII to VWF.

Spectacular clinical results were obtained when this product, designed to emancipate FVIII from the slaving exerted by VWF, started clinical development in the frame of a phase 1-2 study, that I commented with an editorial in 2020.[8] Konkle *et al*.[9] evaluated two different dosages of the new FVIII (25 IU/Kg and 65 IU/Kg) in 16 adults with severe hemophilia A in order to explore not only the degree of FVIII plasma increase and pace of its post-infusion plasma clearance, but also the safety of this highly engineered molecule. The main findings were that both doses increased FVIII in plasma as predicted and, most importantly, that FVIII remained in plasma with a half-life that was up to four times longer than that observed when the same patients were infused a standard FVIII product (Table 1). In addition, this early study assured that the infusion patients of this highly manipulated molecule did not disrupt immune tolerance to FVIII, so that none of them developed anti-FVIII inhibitory alloantibodies. More recently, a phase 3 study of once weekly efanesoctocog alfa administered to 159 patients with severe hemophilia A achieved high plasma FVIII levels (40% or more) sustained for the majority of the week, transformed severe hemophilia into a mild disease and provided superior bleeding prevention in comparison with prior prophylaxis with standard recombinant FVIII.[10,11] The patients with severe hemophilia enrolled in the study were adults and adolescents, but a study in children younger than 12 years is ongoing to obtain regulatory approval for patients with severe hemophilia irrespective of age. This product with an extralong half-life will be a striking breakthrough for the effective implementation of prophylaxis in hemophilia A (Figure 1), because it is expected to match the satisfactory results obtained with the currently available products in hemophilia B. Indeed, it will be feasible to administer efanesoctocog alfa at weekly or longer intervals in the majority of cases, as well as to attain and sustain plasma levels high enough to transform severe hemophilia into a mild disease.

Efanesoctocog is not yet licensed, perhaps because the ongoing pivotal phase 3 study in children was delayed by the SARS-CoV-2 pandemic in terms of rate enrollment. Hence, the role of this disruptive product in the excellent current scenario of multiple weapons already or soon available for the treatment of hemophilia is only speculative at the time being (Figure 1). For instance, we do not know the price, that is very likely to be higher not only than that of standard half-life recombinant products but also of those with an extended half-life, even though the number of yearly needed infusions will be further reduced in number to at least 50 as it happens already in hemophilia B. Other competitors will be the bispecific monoclonal antibody emicizumab, that mimics the coagulant activity of FVIII with the advantage of being administered subcutaneously at weekly or even more spaced intervals (Figure 1).[12] Another option for adult patients with severe hemophilia A is the launch and regulatory approval, at least in Europe, of the gene therapy product valoctogene roxaparvovec,[13] that, however, can only be used in adults but not in children and has a number of drawbacks discussed elsewhere.[14] Other products are in the development pipeline. Fitusiran increases thrombin formation by quenching the naturally occurring anticoagulant antithrombin and can be injected subcutaneously at intervals as spaced as monthly.[14] Concizumab is a monoclonal antibody that is designed to rebalance the defective coagulation of hemophilia patients by inhibiting another naturally occurring anticoagulant, the tissue factor pathway inhibitor.[16]

All in all, striking progress is taking place and more is coming in the treatment of patients with hemophilia, who have now acquired a life expectancy very close to that of male peers without hemophilia.

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