Biologicals 40 (2012) 191–195

Contents lists available at SciVerse ScienceDirect

Biologicals

journal homepage: www.elsevier.com/locate/biologicals

Plasma derivatives: New products and new approaches

Zuben E. Sauna [a], Gouri Shankar Pandey [a], Nisha Jain [b], Ifthekar Mahmood [c], Chava Kimchi-Sarfaty [a], Basil Golding [d,*]

[a] Laboratory of Hemostasis, Division of Hematology, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD 20892, USA
[b] Clinical Review Branch, Division of Hematology, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD 20892, USA
[c] Clinical Pharmacology & Toxicology Branch, Division of Hematology, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD 20892, USA
[d] Laboratory of Plasma Derivatives, Division of Hematology, Center for Biologics Evaluation and Research, Food and Drug Administration, 29 Lincoln Drive, Bethesda, MD 20892, USA

ARTICLE INFO

Article history:
Received 20 October 2011
Accepted 10 November 2011

Keywords:
Hemophilia
Factor VIII
Factor IX
Immunogenicity
Protein therapeutics
Pharmacogenetics

ABSTRACT

The infusion of plasma-derived or recombinant factors to treat bleeding disorders such as hemophila A and B is a success story in the management of a chronic disease. The effectiveness of this approach is however limited by challenges with adverse effects of treatment. The most notable of these are the development of inhibitory antibodies that target the protein therapeutic. The current standard of care for management of hemophiliacs is prophylactic treatment that includes frequent infusions of a Factor VIII product. Failure to comply with the prophylactic regimen is a major hurdle in the management of these patients. We discuss here more recent findings that argue for a pharmacogenetic approach to understanding (and eventually circumventing) immunogenicity. We also review strategies used to bioengineer coagulation factors to extend the half-lives of coagulation proteins. The rapid progress in the last few years to bioengineer coagulation factors in different ways to attain this goal is described. Finally, novel technologies and potential products are emerging that utilize synthetic molecules in lieu of replacement proteins obviating the limitations associated with replacement therapies.

Published by Elsevier Ltd on behalf of International Alliance for Biological Standardization.

1. Introduction

Decreased or absent levels of coagulation factor VIII (FVIII) or factor IX (FIX) result in the most common bleeding disorders hemophilia A and B respectively. The need for medical intervention arises not only because of blood loss following injury but also due to bleeding episodes that occur in the joints leading to deformity and crippling arthritis [1,2]. Attempts to treat bleeding disorders with blood transfusions began in the 19th century but it was only in the 1960s that infusion of concentrates of the missing clotting factor were introduced [3]. The emergence of HIV and hepatitis transmission by plasma-derived concentrates had a devastating effect on patients [4]. These events resulted in the development of recombinant forms of the products and almost all new patients are now treated with such products in the US and many economically developed countries [5]. See Fig. 1A for a time-line showing the development of treatments for bleeding disorders.

Two approaches to coagulation concentrate treatments have been used in the clinic. On demand treatment involves the use of drug only at the time of an acute event to stop the bleeding. Prophylaxis on the other hand is a preventive therapeutic approach where the drug is administered long-term at regular intervals. The prophylactic approach has been shown, in a prospective randomized study to significantly reduce chronic joint damage [6] and is considered optimal care for children with severe hemophilia [6,7].

There is no cure for the hemophilias but replacement therapy permits the successful management of this disorder, both extending the lifespan and quality of life of patients [5]. Moreover, advances in manufacturing technology and the introduction of recombinant products have significantly reduced the risks associated with infectious agents. Despite these improvements there continue to be clinical challenges in the treatment of bleeding disorders (Fig. 1B) and a need for products that can meet these challenges. At present, the most serious complication associated with factor replacement therapy is the development of antibodies that inhibit the function of FVIII or FIX. In addition surveys of practice patterns consistently show that the frequency with which the replacement proteins need to be administered is a significant barrier to following an optimal treatment regimen [8–10].

2. The need for longer-acting drugs

The frequency of infusions of replacement FVIII and FIX constitutes an inconvenience that can significantly affect effective

* Corresponding author. Tel.: +1 301 496 4396; fax: +1 301 402 2780.
E-mail address: basil.golding@fda.hhs.gov (B. Golding).

1045-1056/$36.00 Published by Elsevier Ltd on behalf of International Alliance for Biological Standardization.
doi:10.1016/j.biologicals.2011.11.003

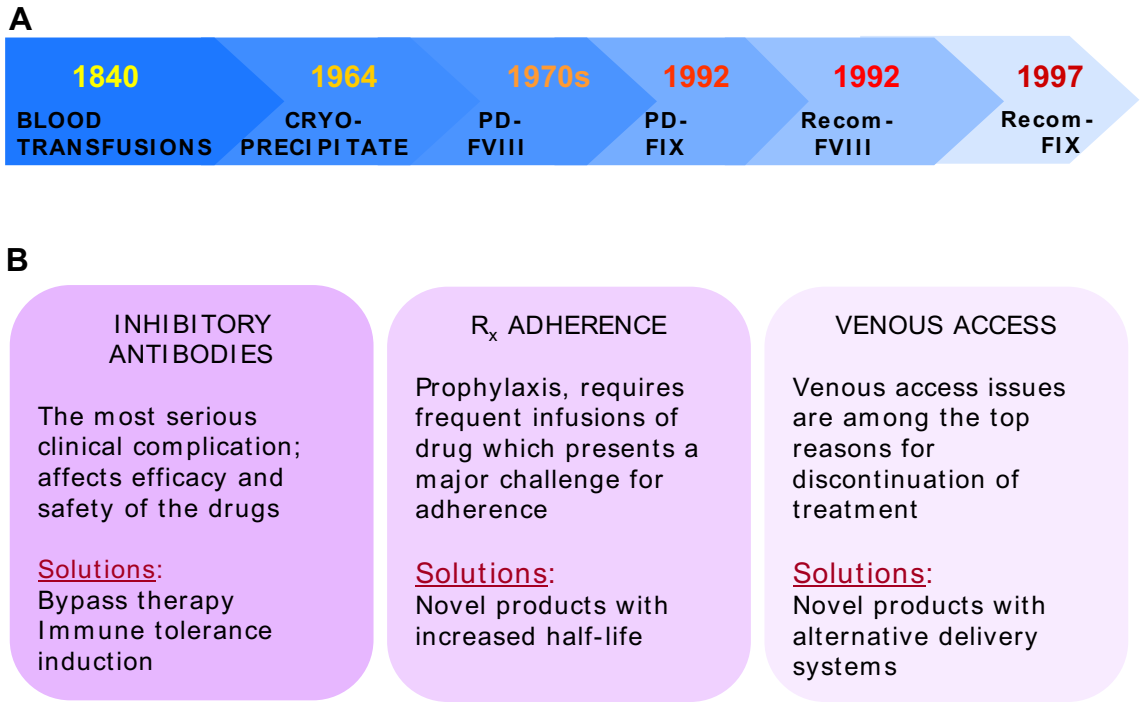

Fig. 1. (A) Time-line showing the evolution of treatments for bleeding disorders. (B) The most important challenges in the treatment of bleeding disorders and unmet medical needs.

prophylaxis [11]. In addition to the inconvenience, frequent infusions present practical problems in children, in whom, venous catheters often need to be placed [12]. The short half-life of FVIII and FIX, 15.3–19.7 h and 16.4–20.8 h, respectively [13,14] necessitates these frequent infusions. Thus, several strategies are being pursued both in academia and industry to bioengineer clotting factors to enhance the half-life (Fig. 2). In general, the goal is to develop protein-drugs that can be administered once weekly (or more infrequently) at a standard dose to maintain a trough factor level above 1% [15].

2.1. PEGylation

Chemical modification of therapeutic proteins with PEG derivatives (PEGylation) is an established technology to increase the half-life of protein therapeutics and such products have gained regulatory approval [16,17]. Preclinical studies and early clinical trials are underway evaluating the effects of PEGylation on both FVIII and rFVIIa [18]. PEGylation can be accomplished by chemical cross-linking of the PEG moieties to exposed amine groups of lysine residues. In the case of clotting proteins such an approach led to partial or complete inhibition of the proteins' procoagulant functions. Even if the reaction can be controlled to yield a functional protein the final product is heterogeneous which presents problems for drug development.

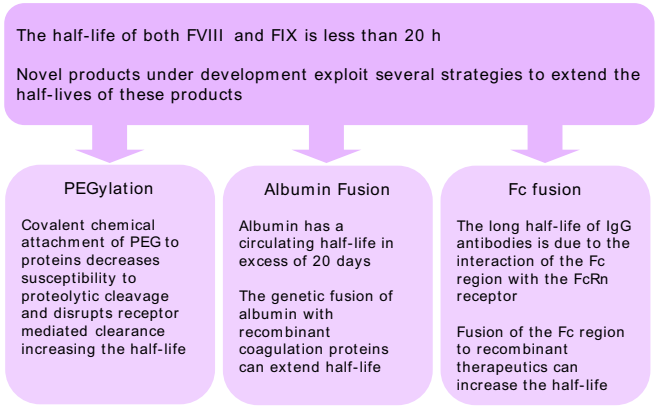

Fig. 2. Strategies currently being pursued to develop longer-acting versions of the coagulation factors, FVIII and FIX.

Site-directed PEGylation is a technology that circumvents this problem by targeting PEG to cysteine residues using PEG-maleimide [19]. Such a targeted approach for PEGylation of FVIII has been developed [20]. In this study a large number of surface-exposed cysteine substitutions were first introduced into FVIII and the specific activities of the novel proteins determined. On the basis of these initial studies, several of the cysteine-substituted molecules were then conjugated through PEG-maleimide attachments and the PEGylated proteins evaluated to select conjugates where PEGylation did not significantly reduce the procoagulant function of the molecule. Subsequent studies in hemophilic mice with di-PEGylated FVIII molecules demonstrated a significantly extended half-life and excellent in vivo hemostatic efficacy. Further evaluation of these promising conjugated proteins is now awaited in large animals and in initial clinical trials.

Some experts have advised a cautious approach to the adoption of these strategies as there is limited information on the long-term use of a PEGylated proteins and how the body disposes of the dissociated PEG. Although PEGylated forms of molecules such as interferon have been used for up to a year in patients, longer-term use of these conjugates has not been assessed, and will need to be kept in mind for hemophilia treatment [15].

2.2. Albumin fusion

Albumin is the most abundant naturally-occurring protein in blood with a circulating half-life in excess of 20 days [21] and its