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Review

Entering new areas in known fields: recombinant fusion protein linking recombinant factor VIIa with recombinant albumin (rVIIa-FP) – advancing the journey

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KEYWORDS

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ABSTRACT

The novel fusion protein linking recombinant factor VIIa with recombinant albumin (rVIIa-FP) is designed to extend the half-life of recombinant factor VIIa (rFVIIa) and improve the care of hemophilia A or B patients with inhibitors. Preclinical studies in various animal models have demonstrated markedly improved pharmacokinetic and pharmacodynamic properties, as well as prolonged retention in the joint tissues, of rVIIa-FP compared with a commercially available rFVIIa (NovoSeven®). A phase I study in healthy volunteers – the first study in the PROLONG-7FP program – confirmed that rVIIa-FP has a good tolerability profile in doses of up to 1,000 μg/kg and has demonstrated enhanced pharmacodynamic activity relative to rFVIIa. The half-life of rVIIa-FP at the highest dose investigated in the study was 8.5 hours, which represents a 3- to 4-fold half-life extension compared with rFVIIa. Encouraging results from preclinical and phase I studies have led to the initiation of clinical studies of rVIIa-FP in patients with congenital hemophilia A or B and inhibitors, and in patients with confirmed factor VII deficiency. The results from these studies are awaited with interest by clinicians and patients alike.

Introduction

Inhibitory antibodies to factor VIII (FVIII) or factor IX (FIX) develop in approximately 30% of previously untreated patients with severe hemophilia A and in 3–5% of previously untreated patients with severe hemophilia B who initiate treatment with coagulation factor concentrates [1–4]. The management of patients who develop high-responding inhibitors (≥5 Bethesda units/mL) frequently includes the use of bypassing agents, such as recombinant factor VIIa (rFVIIa; NovoSeven®) or Factor Eight Bypassing Activity (FEIBA®) [5]. rFVIIa is administered with the aim of providing supraphysiological levels of FVIIa to enhance the rate of thrombin generation on thrombin-activated platelet surfaces in the absence of FVIII or FIX [6]. Although highly effective in treating bleeds in hemophilia patients with inhibitors, the short half-life of rFVIIa (estimated to be 2.3 hours in this population [7]) necessitates intravenous (IV) administration every 2–3 hours to achieve hemostasis [7].

Recombinant fusion protein linking recombinant factor VIIa with recombinant albumin (rVIIa-FP) is a novel fusion protein that has been designed to extend the half-life of rFVIIa with the aim of achieving more effective and convenient care for patients with hemophilia A or B and inhibitors. The molecule is produced by the fusion of "wild-type" rFVIIa to recombinant albumin using a non-cleavable 31-amino-acid glycine–serine linker and expressed as a single moiety by Chinese hamster ovary cells (Figure 1) [8,9]. No modification of the FVIIa amino acid sequence is required to produce rVIIa-FP and, upon activation, the FVII activity provided by rVIIa-FP mirrors that of wild-type rFVIIa [8,9].

Preclinical studies of rVIIa-FP in animal models

The pharmacokinetics (PK) and pharmacodynamics (PD) of rVIIa-FP have been evaluated extensively across various animal models. In one of the first preclinical studies conducted, wild-type rFVIIa, NovoSeven®, rVIIa-FP (all at a dose of 100 μg/kg body weight), or plasma-derived human serum albumin (at a dose of 500 mg/kg body weight) were administered to CD® rats, with FVII and albumin antigen levels measured up to 24 hours postinjection using an enzyme-linked immunosorbent assay [9]. In this study, the half-life of rVIIa-FP was found to be 6.7-fold longer than that of wild-type rFVIIa and 5.8-fold longer than that of NovoSeven® [9]. The recovery (i.e. the percentage recovered 5 minutes after injection) of rVIIa-FP was 47.1% compared with just 19.5% after NovoSeven® and 34.8% after wild-type rFVIIa injection. The combination of an improved recovery, reduced clearance, and prolonged half-life with rVIIa-FP resulted in an area under the curve that was 9.5-fold and 14.5-fold higher with rVIIa-FP than with wild-type rFVIIa and NovoSeven®, respectively [9].

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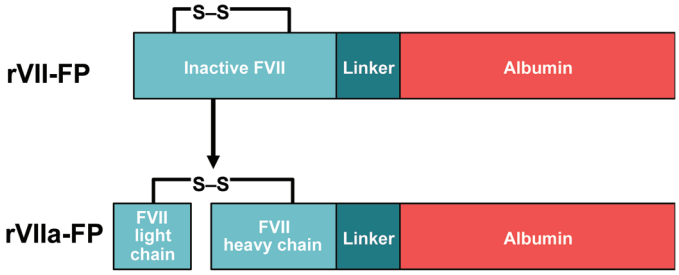

Fig. 1. Design of the recombinant fusion protein linking recombinant factor VIIa with recombinant albumin (rVIIa-FP): designed to extend the half-life of recombinant activated factor VII (rFVIIa) and improve patient care.

Subsequent PK studies comparing single IV doses of rVIIa-FP and NovoSeven® in hemophilia A mice, rats, rabbits, and cynomolgus monkeys confirmed these initial findings and demonstrated enhanced recovery, reduced clearance, and a substantial prolongation of the rFVIIa half-life after the administration of rVIIa-FP compared with NovoSeven® (Figure 2) [10].

The improved PK properties of rVIIa-FP relative to NovoSeven® have translated into enhanced PD activity in animal models [10]. Studies using thrombin generation assay in hemophilia A mice reported prolonged activity and enhanced thrombin generation after the administration of equimolar doses of rVIIa-FP compared with NovoSeven® [10]. The procoagulant activity of rVIIa-FP was also enhanced compared with NovoSeven® in a rabbit model of venous thrombosis [10].

The tissue distribution of rVIIa-FP and NovoSeven® has recently been studied in rats using quantitative whole-body and knee-joint autoradiography [11]. In this study, Sprague–Dawley rats received a single IV injection of tritium-labeled rVIIa-FP 10 mg/kg (n=8) or NovoSeven® 1.6 mg/kg (n=4) and underwent autoradiography for 240 hours or 24 hours, respectively, post-administration. The tissue distribution patterns observed for both products were similar, with both penetrating well into many tissues, including the kidney, bone endosteum, bone marrow, spleen, muscles, liver, and skin. NovoSeven® and rVIIa-FP penetrated rapidly into knee-joint structures, with the highest concentrations found in the calcified cartilage, endosteum, and periosteum. A detailed analysis of the knee joint showed high levels of radioactivity within 15 minutes of administration of both rVIIa-FP and NovoSeven® (Figure 3). However, by 24 hours after administration of NovoSeven®, levels were almost undetectable in the knee. In contrast, radioactivity was still detectable up to 120 hours after administration of rVIIa-FP, indicating markedly prolonged tissue retention [11].

Phase I study of rVIIa-FP in healthy volunteers

A phase I safety and PK study of rVIIa-FP in healthy volunteers has also been completed as part of the PROLONG-7FP clinical development program [12]. The study was a prospective, double-blind, placebo-controlled study that enrolled 40 healthy, young (aged

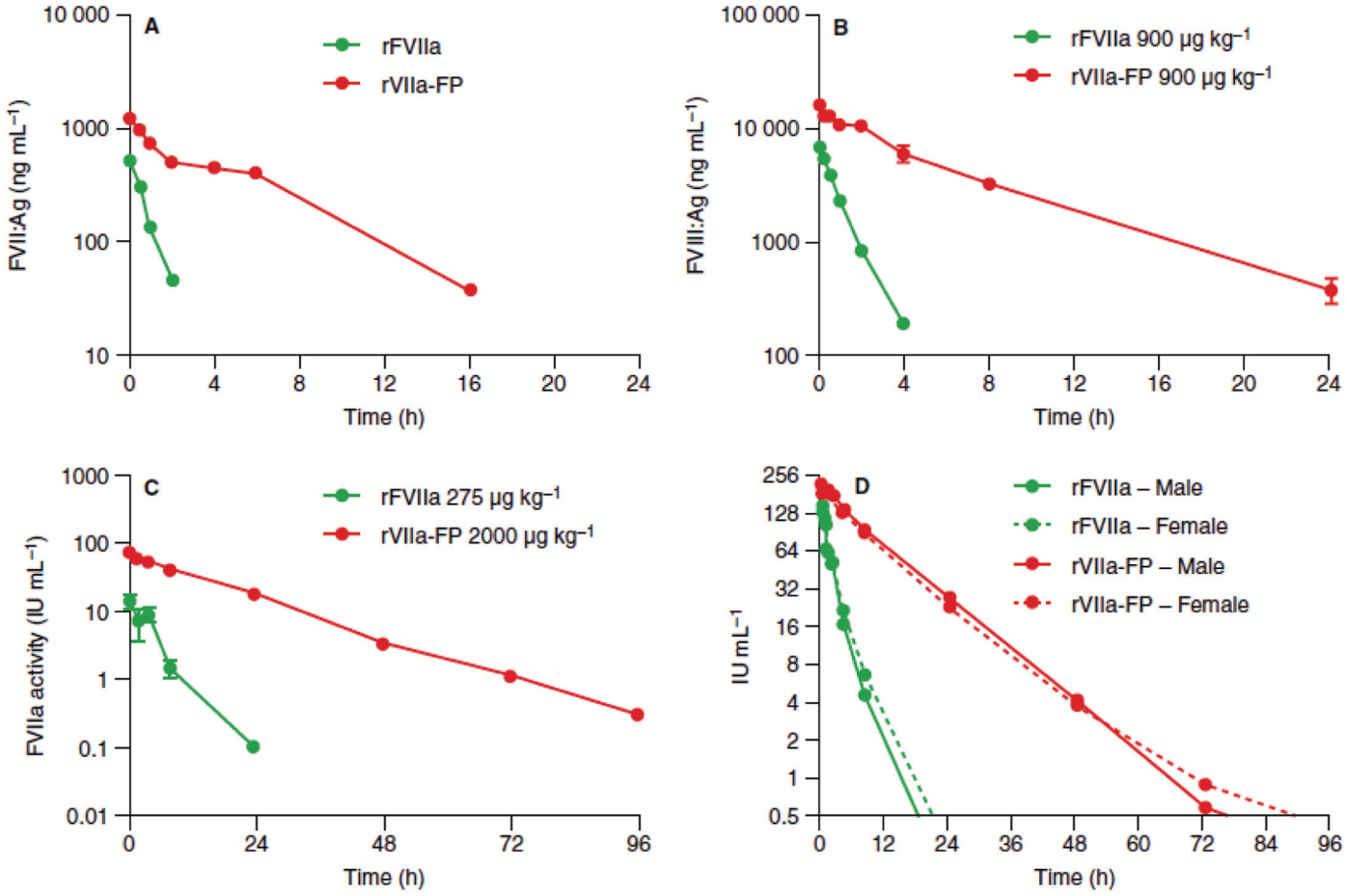

Fig. 2. Plasma concentration–time profiles of recombinant fusion protein linking recombinant factor VIIa with recombinant albumin (rVIIa-FP) and recombinant activated factor VII (rFVIIa; NovoSeven®) in (A) hemophilia A mice, (B) rats, (C) rabbits and (D) cynomolgus monkeys [10]. Data shown are means, except for mice (plasma pool) and monkeys, where the curve for each animal is shown. FVII:Ag, factor VII antigen. Reproduced from Zollner S et al. Pharmacological characteristics of a novel, recombinant fusion protein linking coagulation factor VIIa with albumin (rVIIa-FP). J Thromb Res 2014; 12: 220–228. CC-BY-NC-ND © 2013 International Society on Thrombosis and Haemostasis.