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REVIEW

Recombinant factor XIII and congenital factor XIII deficiency: an update from human and animal studies

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Abstract: Factor XIII (FXIII) is a protransglutaminase composed of two catalytic A subunits and two carrier B subunits. An intracellular form of FXIII is present in monocytes/macrophages and platelets as a homodimer of two A subunits. Following activation by thrombin, FXIII becomes plasma transglutaminase, which crosslinks γ-glutamyl-ε-lysine residues of fibrin chains and thereby stabilizes the fibrin clot. FXIII deficiency results in a moderate to severe hemorrhagic disorder, abnormal wound healing in about 30% of patients, and recurrent abortion in homozygous females. More than 800 cases of FXIII deficiency have been reported, most of them due to mutation in the *FXIII-A* gene, resulting in FXIII-A deficiency. Among mutations causing *FXIII-A* deficiency, 50% are missense mutations. Only 16 mutations in the *FXIII-B* gene have been published. Routine laboratory tests are normal in patients with FXIII deficiency, and the diagnosis is established by demonstration of decreased FXIII activity and antigen. Plasma-derived, virus-inactivated factor XIII concentrate is the treatment of choice. The low plasma levels of FXIII (about 5%) required to control bleeding and its long half-life make monthly prophylactic therapy feasible. Recently, recombinant FXIII concentrate with a half-life similar to that of native FXIII has been developed and tested in a multinational clinical study. This new product appears to be safe and appropriate for lifelong prophylactic treatment of patients with FXIII-A deficiency.

Keywords: recombinant FXIII concentrate, FXIII deficiency

Factor XIII

Factor XIII (FXIII) belongs to the family of protransglutaminases and is the final enzyme of the blood coagulation cascade. Following activation by thrombin in the presence of calcium, FXIII becomes active transglutaminase that crosslinks γ-glutamyl-ε-lysine residues of fibrinogen chains, leading to increased stability of the fibrin clot.[1] Activated FXIII also crosslinks antiplasmin to fibrin, making the clot more resistant to fibrinolysis by plasmin.[2] Plasma factor XIII (pFXIII) is an Mr ~340,000 heterotetramer composed of two catalytic A subunits (FXIII-A_2; Mr ~82,000) and two carrier B subunits (FXIII-B_2; Mr ~76,500) linked together through noncovalent bonds.[3] An intracellular form of FXIII (cFXIII) is present in monocytes/macrophages and macrophages/platelets as a homodimer of two A subunits (cFXIII-A_2). The first 37 amino acids at the N-terminus of FXIII-A comprise an activation peptide (AP-FXIII). Thrombin cleaves the R37-G38 peptide bond and then, in the presence of Ca^{2+}, the B subunits dissociate and the dimer of truncated FXIII-A (FXIII-A_2') assumes an enzymatically active configuration (G38-FXIII-A_2*) exposing an active Cys 314 residue.[3] Fibrin polymers are an important cofactor to generate activated FXIII (FXIIIa).[4]

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The three-dimensional structure of FXIII-A determined by X-ray crystallography disclosed that the A subunit is divided into four sequential domains: the β-sandwich (Glu 43 to Phe 184), the catalytic core (Asn 185 to Arg 515), and two barrel domains (Ser 516 to Thr 628 and Ile 629 to Arg 727).[5] The three-dimensional structure of FXIII-A provides further information concerning the structure-function relationship of FXIII. It was demonstrated that Cys 314 forms a hydrogen bond with His 373, while the other nitrogen atom in the histidine ring forms a hydrogen bond with Asp 396.[5]

The FXIII-B_2 functions as a carrier protein for FXIII-A_2,[6] stabilizing the A subunits in the circulation and regulating calcium-dependent activation of factor XIII. FXIII-B is composed of ten homologous consensus ("sushi") repeats.[7] Each repeat is approximately 60 amino acids in length and contains four disulfide bonds, with Cys 1 linked to Cys 3 and Cys 2 linked to Cys 4.

The gene for FXIII-A is located on chromosome 6p24–p25.[8,9] The gene spans 177 kb and is composed of 15 exons. Exon I consists of the 5′ noncoding region, and the activation peptide (amino acid 1–37) is encoded by exon II.[9] The gene for FXIII-B has been localized to chromosome 1q31–q32.1,[10] and spans 28 kb composed of 12 exons. The first exon encodes the leader sequence whereas exons II through XI each encode a single "sushi" repeat.[10]

FXIII-A is synthesized in megakaryocytes and during platelet formation is packed into newly formed platelets.[11] In addition, FXIII-A has been demonstrated in monocytes, tissue macrophages/histiocytes, the liver, chondrocytes, and osteoblasts.[11–15] FXIII-B is synthesized in the liver[13] and secreted as a dimeric form (FXIII-B_2) into plasma.[16] Assembly of the factor XIII A and B subunits probably occurs in the circulation. The average plasma concentration of the A_2B_2 heterotetramer is approximately 22 μg/mL and its half-life is 9–14 days.[17]

FXIIIa catalyzes the formation of peptide bonds between adjacent molecules of fibrin monomer and thus imparts chemical and mechanical stability to a clot. In addition, a number of other proteins are also substrates for FXIIIa, including factor V, plasminogen activator inhibitor-2, collagen, thrombospondin, von Willebrand factor, vinculin, vitronectin, fibronectin, actin, myosin, and lipoprotein (a).[3]

Consequences of FXIII deficiency in animal models

In addition to the fundamental role of FXIII in hemostasis, its importance in thrombosis and wound healing is emphasized in FXIII deficiency, which is characterized by bleeding, abnormal wound healing, and spontaneous miscarriage in females. An animal model of factor XIII deficiency, ie, FXIII-A knockout mice, manifests as intrathoracic, intraperitoneal, and subcutaneous hemorrhage.[18] Impaired tissue repair was observed in FXIII-A knockout mice in the left ventricles after myocardial infarction, while high FXIII activity was observed within the infarct of wild-type mice.[19] In male FXIII-A knockout mice, fibrosis of the myocardium with deposition of hemosiderin, a marker of hemorrhage, was observed.[20] Cutaneous wound closure was reduced by almost 30%, with necrotic tissue formation and delayed re-epithelialization in FXIII-A knockout mice compared with wild-type mice.[21] Treatment with FXIII has been shown to be effective in correcting clinical manifestations in FXIII-A knockout mice, supporting the importance of FXIII in thrombus formation and wound healing.[18,21,22] Similarly, in rats with experimentally induced colitis, lesion severity was significantly reduced when treated with FXIII.[23] Reduced edema formation in reperfused ischemic rat heart was observed following FXIII administration ex vivo. Further, treatment with FXIII reduced vascular leakage in a guinea pig model of antiserum-induced vascular damage.[24] In addition to its role in wound healing, FXIII also promotes angiogenesis, and it has been shown that FXIII treatment promotes angiogenesis in rabbit cornea and in a heterotopic heart allograft in FXIII-A deficient mice.[25,26]

Congenital FXIII deficiency

The first case of severe congenital FXIII deficiency was described more than 50 years ago in a Swiss boy with bleeding diathesis and impaired wound healing.[27] To date, about 800 patients have been diagnosed with FXIII deficiency.[1] Congenital FXIII deficiency is a severe bleeding disorder transmitted in an autosomal recessive manner. Typical bleeding manifestations include umbilical stump bleeding during the first few days of life, postoperative bleeding, and intracranial hemorrhage, which is observed more frequently in FXIII deficiency than in other inherited bleeding disorders. Other bleeding manifestations include ecchymoses, hematomas, and prolonged bleeding following trauma.[28] Hemarthroses and bleeding into the muscles are less common than in the hemophiliacs.

Habitual abortion is commonly observed in affected females and in mice deficient in FXIII-A.[29] The mechanism/s underlying this effect of FXIII might be due to intrauterine bleeding.[29] In addition, formation of the cytotrophoblastic shell is impaired in affected homozygous women, probably due to deficient fibrin/fibronectin crosslinking at the

implantation site leading to detachment of the placenta and miscarriage.[30]

Delayed wound healing was reported in approximately 30% of FXIII-deficient patients.[31] The significance of FXIII in wound repair is based on several lines of evidence: sporadic reports demonstrate the beneficial effect of FXIII concentrates in clinical situations such as inflammatory bowel disease, graft versus host colitis, and healing of surgical wounds;[32–34] FXIII can modulate the composition and stability of the fibrin network; FXIII enhances migration, proliferation,[35] and phagocytosis[36] of monocytes and fibroblasts, which are essential components of the tissue repair process; and, finally, FXIII facilitates new blood vessel formation in both in vivo and in vitro models.[25,37] Since angiogenesis is an essential process for tissue repair and remodeling, it is possible that by its proangiogenic activity FXIII contributes further to the healing process. The diverse activities of FXIII in tissue repair are summarized in Figure 1.[32]

Most congenital FXIII deficiency is caused by FXIII-A subunit deficiency, which occurs at a frequency of approximately one in two million.[38] Congenital deficiency of the FXIII-B subunit is a rare cause of clinically significant FXIII deficiency.[39] Among 104 reported mutations causing FXIII-A deficiency, 50% are missense mutations, 26 are deletions/insertions, nine are splice site mutations, and ten are nonsense mutations. Only 16 mutations have been reported in the *FXIII-B* gene.[39] An updated list of mutations is available on the Internet (http://www.f13-database.de).

Diagnosis

The prothrombin time and activated partial thromboplastin time are normal in factor XIII deficiency. Patients deficient in FXIII-A lack plasma and platelet FXIII-A. In patients deficient in FXIII-B, the B subunit is absent in plasma while plasma FXIII-A is decreased to 5%–40% but normal in platelets.[40]

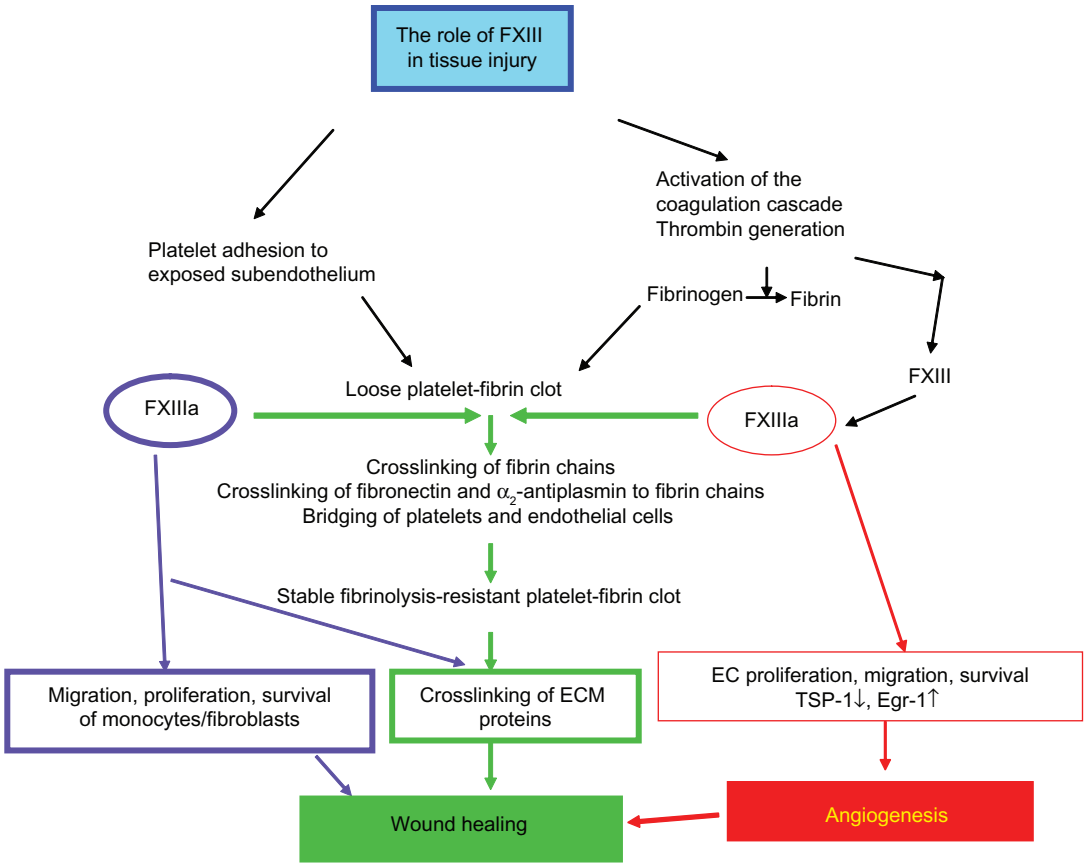

Figure 1 Pleiotropic role of FXIII in tissue repair. During the first stages of wound healing, formation of a fibrin clot is stabilized by (FXIIIa). At this stage, the platelet-rich thrombus is anchored to the vessel wall to prevent further bleeding. FXIIIa subsequently crosslinks adjacent fibrin chains and fibrinolysis inhibitors such as α2-antiplasmin and plasminogen activator inhibitor-2 to fibrin to form a stable platelet-fibrin clot that is resistant to fibrinolysis. In addition, FXIIIa mediates the incorporation of fibronectin and other extracellular matrix proteins into the fibrin clot to form a provisional matrix for migration and proliferation of macrophages and fibroblasts into the wound area. FXIIIa further facilitated new vessel formation by direct stimulation of endothelial cell migration, proliferation, and survival by upregulation of Egr-1 and c-Jun and downregulation of TSP-1, thereby providing nutrients for the newly formed tissue.

Abbreviations: FXIII, Factor XIII; FXIIIa, thrombin-activated Factor XIII; EC, endothelial cell; ECM, extracellular matrix; TSP-1, thrombospondin-1; Egr-1, early growth response protein 1.

Historically, the diagnosis of FXIII deficiency was established by confirming decreased FXIII activity using tests that demonstrated increased clot solubility in 5 M urea, dilute monochloroacetic acid, or acetic acid. However, these tests have substantial disadvantages: they detect only the most severe FXIII deficiencies (<0.5%–2% activity); they are poorly standardized; and their sensitivity depends on the features and concentration of the solubilizing agent as well as on the concentration of fibrinogen. Thus, solubility tests must not be used as screening tests for FXIII deficiency, and a quantitative functional assay for the determination of plasma FXIII activity should be used instead. FXIII activity is determined quantitatively by measuring the incorporation of fluorescent or radioactive amines into proteins.[41] Quantitative photometric assays are not accurate at levels of FXIII activity between 0% and 10% of normal because they overestimate FXIII activity, thus misdiagnosing severe cases of FXIII deficiency. For this reason, a plasma blanking procedure is recommended[42] and modified sensitive photometric assays with a detection limit >0.6% have been developed recently (Reanalker, Budapest, Hungary). Specific enzyme-linked immunosorbent assays have also been developed to establish FXIII-A, FXIII-B, and FXIII-A_2B_2 antigen levels.[43]

Treatment

The severity of bleeding symptoms in congenital FXIII deficiency is the main reason for preventive regular replacement therapy. Replacement therapy for factor XIII deficiency is highly satisfactory because of the small quantities of factor XIII needed for effective hemostasis (~5%) and the long half-life of FXIII (9–14 days). Until recently, only plasma-derived sources of FXIII have been available,[44,45] including fresh frozen plasma, cryoprecipitate, and a plasma-derived, virally inactivated FXIII concentrate. Recently, a recombinant FXIII concentrate has been developed (described below). Fresh frozen plasma and cryoprecipitate are widely available but carry an increased risk of blood-borne infections, allergic reactions, and have uncertain potency and unknown pharmacokinetics. Plasma-derived FXIII concentrate (Fibrogammin® P) underwent a virus-inactivated procedure; however, this virucidal procedure does not eliminate the possible transmission of non-lipid-enveloped pathogens such as parvovirus B19 and hepatitis A. In addition, since there is currently no screening test for blood donors for the prion that causes variant Creutzfeldt–Jakob disease it should be kept in mind that prions are not destroyed by current virucidal methods. The cost of the recombinant concentrate is higher than that of cryoprecipitate or FFP, but lifelong exposure to a recombinant product devoid of any mammalian proteins has a substantial advantage with regard to patient safety.

Prophylactic therapy with Fibrogammin P at a dose of 10–20 U/kg every 4–6 weeks has been successful in achieving normal hemostasis.[44] During pregnancies, more frequent injections are necessary to prevent habitual abortion.[45] In a small study of seven patients, the mean annual number of spontaneous bleeds was 2.5 events per year prior to Fibrogammin P prophylaxis and 0.2 events per year during prophylaxis.[46] Yoshida et al reported that bleeds markedly decreased from 4.2±1.5 per year to 0.2±0.2 per year, with no life-threatening hemorrhage, including intracerebral hemorrhage, in four patients given regular replacement therapy with Fibrogammin P every 4 weeks for 10–19 years.[47] Finally, a recent prospective study showed that on prophylaxis with Fibrogammin P, the majority of patients with FXIII deficiency had no hemorrhage, supporting the effectiveness of prophylactic treatment.[48]

Recently, it was shown that treatment with FXIII concentrate Fibrogammin P in patients with congenital FXIII-A deficiency increases platelet adhesion to fibrinogen by almost 30%, thereby improving further platelet function.[49] This may have important therapeutic implications for the use of FXIII concentrates. In addition to the well established effect of FXIII on secondary hemostasis (clot stability), FXIII concentrate might also enhance primary hemostasis (platelet function) in patients with congenital FXIII-A deficiency.

A new recombinant FXIII (rFXIII) homodimer (rFXIII-A_2), originally developed by Zymo Genetics Inc (Seattle, WA, USA), and later transferred to Novo Nordisk A/S (Copenhagen, Denmark), has been manufactured in *Saccharomyces cerevisiae* (yeast) and contains no human/mammalian products. rFXIII-A_2 homodimers associate in plasma with endogenous FXIII-B to form the stable heterotetramer FXIII-A_2B_2.

Clinical studies conducted with rFXIII concentrate are summarized in Table 1. Safety, pharmacokinetics, and immunogenicity have been studied in healthy volunteers and in patients following cardiac surgery (Table 1).[50–52] In a Phase I clinical trial, rFXIII had a half-life similar to that of native FXIII.[53] This new product was found to have a good safety profile and is appropriate for development for monthly prophylactic administration in patients with FXIII-A subunit deficiency.[53] A multinational, open-label, single-arm, multiple-dosing, Phase III prophylaxis trial was undertaken to evaluate the efficacy and safety of rFXIII for the prevention of bleeding in congenital FXIII-A subunit deficiency.[54] The estimated half-lives of the FXIII-A_2 subunit, FXIII-A_2B_2,

Table 1 Clinical studies with recombinant FXIII

Trial ID	Title	Doses	n	Reference
UKHV-1	Randomized, placebo-controlled, single-dose, double-blind study of the safety and pharmacokinetics of rFXIII in healthy volunteers	0, 2, 5, 10, 25, 50 U/kg	50 healthy subjects	Reynolds et al[50]
112C01	A randomized, placebo-controlled, double-blind, multidose study of the safety and pharmacokinetics of rFXIII administration in healthy volunteers	0, 10, 25 U/kg daily for 5 days	24 healthy subjects	Visich et al[51]
CD1.3 Phase I trial	Escalating-dose study of the safety and pharmacokinetics of rFXIII in patients with congenital FXIII-A deficiency	2, 6, 20, 50, 75 U/kg	11 patients	Lovejoy et al[53]
F13CARD-1660	Randomized, double-blind, placebo-controlled, dose escalation trial on safety and pharmacokinetics in patients following cardiac surgery	12, 30, 60, 89, 119 IU/kg equivalent to 10, 25, 50, 75, 100 IU/kg	50 patients	Levy et al[52]
F13CD-1725 Mentor™-1; Phase III trial	Multicenter, multinational, open-label, single-arm, multiple dosing (prophylaxis) trial in patients with congenital FXIII-A deficiency	35 IU/kg	41 patients	Inbal et al[54]

and FXIII activity were similar to those reported for plasma derived FXIII-containing products,[55] and for rFXIII in the previous Phase I study.[53]

With regard to efficacy, no spontaneous treatment-requiring bleeds or intracranial hemorrhage occurred during the rFXIII treatment period. Bleeds requiring treatment were observed in only four of 41 participating patients, all of them due to trauma. The bleeding frequency was significantly lower than the rate of 2.91 bleeds requiring treatment per year in patients receiving on-demand treatment in data collected retrospectively.

No safety issues were raised besides development of transient, low-titer, non-neutralizing anti-rFXIII antibodies in four of 41 patients, who continued to be treated with either rFXIII or plasma-derived FXIII. The presence of these non-neutralizing antibodies was not associated with any treatment-requiring bleeds, changes in FXIII pharmacokinetics, allergic reactions, or specific genotype. Further, the antibodies declined below the detection limit in all patients, despite repeated exposure to rFXIII or other FXIII-containing products, indicating that they were not clinically significant. Taken together, this study demonstrated that rFXIII as monthly replacement therapy is efficacious and safe for prophylactic treatment in patients with congenital FXIII-A subunit deficiency.[54] Currently, rFXIII concentrate (NovoThirteen®, Novo Nordisk) was approved for the treatment of FXIII-A deficiency by the European Medicine Agency for the countries in the European Common Market and Canada.

In summary, all the symptoms of FXIII deficiency can be prevented or controlled by lifelong monthly prophylactic treatment with FXIII concentrates, thereby enabling a normal and active life for every patient.

Disclosure

The author reports no conflicts of interest in this work.

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