

# Inhibitors in Patients with Congenital Bleeding Disorders Other Than Hemophilia

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## Abstract

The most worrying complication of replacement therapy for severe hemophilia A and B is currently the occurrence of inhibitory alloantibodies against infused factor VIII and factor IX, respectively. Inhibitors compromise the management of hemorrhage in affected patients, with a considerable increase in complications, disability, and costs. While these alloantibodies have been extensively studied in the past years in hemophilia A and B, those occurring in patients with other inherited bleeding disorders are less well characterized and still poorly understood, mostly due to the rarity of these hemorrhagic conditions. This narrative review will deal with inhibitors arising in patients with inherited bleeding disorders other than “classical” hemophilia, focusing in particular on those developing in patients with congenital deficiency of coagulation factor V, factor VII, factor XI, and factor XIII.

## Keywords

- ▶ inherited bleeding disorders
- ▶ alloantibodies
- ▶ congenital
- ▶ inhibitors

The most serious complication of treatment with coagulation factor concentrates in patients with congenital hemophilia is development of alloantibodies against the deficient coagulation factor (F), namely, VIII (FVIII; hemophilia A) or IX (FIX; hemophilia B).<sup>1–5</sup> Indeed inhibitory alloantibodies, which develop in up to one-third of previously untreated patients with severe hemophilia A and up to 5 to 6% of patients with severe hemophilia B, neutralize the coagulant effect of factor replacement therapy, therefore requiring a shift toward treatments based on FVIII- and FIX-bypassing agents.<sup>6–8</sup> As a consequence, inhibitors preclude the access of persons with hemophilia to safe and effective standards of care, predisposing them to increased risk of morbidity and permanent disability which, ultimately, negatively influences their quality of life.<sup>7</sup> The management of hemophilia A patients with inhibitors is particularly challenging for physicians operating at hemophilia treatment centers (HTCs), as they are frequently forced to make critical decisions based on their own experi-

ence rather than on evidence-based data.<sup>9</sup> Due to the heavy social, health, and economic burden of inhibitors,<sup>3</sup> it is not surprising that several investigators have devoted their research in the last decade on understanding the pathogenic mechanisms of inhibitors to predict and, possibly, prevent their development.<sup>9</sup> However, while such investigation has been focused mainly on patients with hemophilia A and B, little is known pertaining to the inhibitors occurring in persons with the rarer congenital bleeding disorders due to defects of the other clotting factors. In this narrative review, we summarize the current knowledge on alloantibodies complicating replacement treatment in patients with inherited deficiency of coagulation FV, FVII, FXI, and FXIII. Alloantibodies occurring against von Willebrand factor in patients with von Willebrand disease and patients with Glanzmann's thrombasthenia and other inherited platelet disorders will not be discussed here, as these are the subjects of two other reviews in this issue of the journal.<sup>10,11</sup>

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## Search Methods

We reviewed the medical literature for published studies on alloantibodies in patients with inherited bleeding disorders other than hemophilia A or hemophilia B. The MEDLINE electronic database was searched without temporal limits using English language restriction. The Medical Subject Heading and key words used were: “alloantibodies,” “inhibitors,” “inherited,” “congenital,” “bleeding disorders,” “hemorrhagic disorders,” “coagulation factors deficiency,” “factor V (FV),” “factor XI (FXI),” “factor VII (FVII),” and “factor XIII (FXIII).” We also screened the reference lists of most relevant review articles for further studies not captured in our initial literature search. Search terms were also applied to abstracts from the latest international congresses on hemostasis and thrombosis and hematology.

## Alloantibodies in Congenital FV Deficiency

### Characteristics of Congenital FV Deficiency

FV is a 249 kDa glycoprotein encoded by *F5* gene located on chromosome 1 and synthesized by megakaryocytes and hepatocytes.<sup>12</sup> Approximately 20% of circulating FV is contained in platelets.<sup>13</sup> Once activated by thrombin, FVa acts as a cofactor for FXa in the conversion of prothrombin to thrombin.<sup>14</sup> Notably, as FV also downregulates FVIII activity, an FV deficiency may result in a thrombotic tendency.<sup>15,16</sup> Most cases of FV deficiency are characterized by the concomitant deficiency of FV activity and antigen levels (type I deficiency), while a quarter of them have normal antigen levels, suggesting the presence of a dysfunctional protein (type II deficiency).<sup>12</sup> FV deficiency is inherited in an autosomal recessive manner and has an estimated prevalence of approximately 1:1,000,000.<sup>17–19</sup> The first causative mutation in the *F5* gene leading to a severe FV deficiency was discovered nearly 20 years ago<sup>20</sup> and there are currently more than 200 cases described so far with more than 100 DNA alterations reported, including nonsense and missense mutations, insertions, deletions, and splice-site mutations.<sup>21</sup> Two-thirds of all mutations causing FV deficiency are nonsense mutations in the *FV* gene. One-third of mutations causing FV deficiency introduce premature stop codons in the *FV* gene, either as nonsense mutations or as small out-of-frame insertions or deletions. Many new missense mutations, clustered in the A and C domains, have been described in recent years and now represent nearly 50% of all reported mutations. In most cases, these mutations affect secretion of FV, thus substantially reducing antigen levels (type I deficiency).<sup>21</sup> The fact that most patients carry a unique mutation which is not found in other FV-deficient patients confirms the remarkable allelic heterogeneity of this disease.<sup>22</sup> The initial identification of congenital FV deficiency may be based on the demonstration of the prolongation of both prothrombin time (PT) and activated partial thromboplastin time (aPTT), and the diagnosis by identification of reduced FV activity, usually determined by modified one-stage PT-based clotting assays. To distinguish qualitative from quantitative FV deficiency, a plasma FV antigen determined by immunoassay is required.<sup>23</sup> Congenital FV deficiency can be distinguished from

acquired FV deficiency, in most cases due to FV autoantibodies occurring after exposure to bovine FV present in topical thrombin,<sup>24</sup> by noncorrection in PT and aPTT mixing studies in subjects without previous bleeding history.

Frequent symptoms in patients with FV deficiency are epistaxis and menorrhagia, which occur in approximately 50% of cases. Other, less common symptoms, include hemarthroses and hematomas, which occur in approximately 25% of patients, whereas life-threatening episodes in the central nervous system and gastrointestinal tract are rare (6%).<sup>25–27</sup>

Pertaining to the treatment, there is no FV concentrate available, and FV is not present in significant amount in cryoprecipitate or prothrombin complex concentrates.<sup>28</sup> Thus, replacement therapy of FV is only achieved through fresh frozen plasma, preferably virus inactivated.<sup>29–34</sup> Due to their relative content of FV, platelet transfusions have also been successfully used for the management of FV-deficient patients.<sup>35</sup>

### Anti-FV Alloantibodies

Development of alloantibodies against infused FV is a potential complication of replacement therapy with fresh frozen plasma in patients with severe congenital FV deficiency.<sup>28</sup> Although very few cases have been reported in the literature so far,<sup>36–41</sup> the incidence of this adverse event could be underestimated, especially if low-titer transient inhibitors are considered.<sup>42</sup> For instance, Fratantoni and colleagues<sup>36</sup> described an 8-year-old girl with hereditary FV deficiency who developed an IgG class anti-FV alloantibody after treatment with fresh frozen plasma for several years. It is, however, possible that the FV inhibitor developed earlier, during the first few plasma transfusions, because of a noted initial partial correction of prolonged coagulation profile after fresh frozen plasma transfusions. Subsequently, as the inhibitor titer increased, more frequent plasma transfusions failed to improve the prolonged PT and aPTT. Similarly, Mazzucconi and colleagues<sup>37</sup> reported the case of a female patient with severe congenital FV deficiency who became refractory to plasma infusion due to the development of a low-titer anti-FV antibody. Salooja and colleagues<sup>38</sup> reported another case of neonatal intracranial hemorrhage associated with severe congenital FV deficiency complicated by an FV inhibitor (0.6 Bethesda units [BU]), successfully managed by solvent detergent-treated fresh frozen plasma and platelet concentrate infusion. Lee and colleagues<sup>39</sup> reported the dramatic case of an 18-day-old Indian infant with severe FV deficiency and FV inhibitor (2.4 BU) with intracranial hemorrhage. Repeated transfusions of fresh frozen plasma and platelet concentrates, administrations of immunosuppressive therapy (prednisolone and cyclophosphamide), and intravenous immunoglobulin (IVIG) failed to normalize the coagulation profiles. Exchange transfusion followed up by administrations of activated prothrombin complex and transfusions of fresh frozen plasma and platelet concentrates caused a temporary normalization of coagulation profile, enabling an insertion of a ventriculoperitoneal shunt for progressive hydrocephalus. The treatment was, however, complicated by thrombosis of the left brachial artery and the child finally died from another episode of intracranial hemorrhage 10 days thereafter. Divanon and colleagues<sup>40</sup> reported the case of a 19-year-old man with severe

congenital FV deficiency and a high-titer (6 BU) inhibitor who was treated with single donor leukocyte-depleted platelet concentrate with a consequent anamnestic response (FV inhibitor rose up to 30 BU). Thus, the patient was successfully treated with recombinant activated factor VII (rFVIIa, bolus injections of 80 µg/kg at 3 hourly intervals on the first day, at 4 hourly intervals on the second day and then two daily boluses). Finally, Perez Botero and colleagues<sup>41</sup> described the case of a 67-year-old man with congenital FV deficiency and a high-titer FV inhibitor level with recurrent gastrointestinal bleeding due to arteriovenous malformations successfully treated with thalidomide after endoscopic, hemostatic (activated prothrombin complex concentrate), and hormonal (danazol) treatment failed. As immune tolerance induction (ITI) treatment was impracticable due to the high dose of fresh frozen plasma required, an alternative approach with high-dose corticosteroids and rituximab was attempted, resulting in inhibitor eradication.

In summary, the data available on the characteristics of alloantibodies against infused FV in congenital FV deficiency are scanty (►Table 1), and most information regarding their management are derived from reports of acquired FV inhibitors.<sup>43–45</sup> Thus, for inhibitor eradication, various immunosuppressive agent-based protocols have been suggested.<sup>45</sup> Pertaining to the treatment of bleeding, a large volume of fresh frozen plasma, necessary to overcome the inhibitor and produce an effective hemostatic effect, and platelet concentrates represent the mainstay of the treatment of bleeding in these complicated cases. In particular, transfusion of platelet concentrates should be considered as initial therapy, considering that FV in platelets, unlike that circulating in plasma, is protected from the neutralization of the antibody, being

delivered directly to the site of injury.<sup>46,47</sup> Also, the transfusion of platelets decreases the risk of circulatory overload associated with the transfusion of the large volume of plasma. In patients, refractory to repeated platelet transfusions, the administration of rFVIIa could be beneficial.<sup>40</sup> The main advantages of this recombinant hemostatic agent in such clinical setting include the efficacy being independent of the inhibitor titer and the lack of anamnestic response. In patients with a life-threatening bleeding tendency, an immediate reduction of the FV inhibitor titer by immunoadsorption or plasmapheresis with subsequent administration of fresh frozen plasma with or without platelet concentrates might be the best therapeutic approach.

## Alloantibodies in Congenital FVII Deficiency

### Characteristics of Congenital FVII Deficiency

Factor VII is a 50 kDa vitamin K-dependent glycoprotein that circulates in plasma in two forms (99% as a single chain inactive form and 1% as an active two-chain form). FVII, encoded by the *F7* gene located on chromosome 13, plays a fundamental role in the initiation of coagulation through its interaction with tissue factor.<sup>48,49</sup> FVII deficiency is inherited with an autosomal recessive pattern (estimated prevalence 1:500,000).<sup>49</sup> Circulating levels of FVII coagulant activity (FVII:C) and FVII antigen (FVII:Ag) are influenced by several genetic and nongenetic factors (age, sex, cholesterol, and triglyceride levels), and it is also well known that *FVII* polymorphisms modulate FVII levels.<sup>50</sup> Most patients have concomitantly low levels of FVII:C and FVII:Ag (type 1), but other cases are characterized by normal or moderately low levels of FVII:Ag and much lower levels of FVII:C (type 2).<sup>51</sup> The molecular basis of FVII deficiency

**Table 1** Main characteristics and management of alloantibodies in congenital FV, FXI, and FXIII deficiencies (data derived from literature analysis)

Alloantibody	Congenital FV deficiency	Congenital FVII deficiency	Congenital FXI deficiency	Congenital FXIII deficiency
Class	IgG	IgG	IgG	IgG, most frequently directed against FXIII-A subunit
Anaphylaxis	No	No	No	No
Titer	Reported cases of low and high inhibitor titer. Anamnestic response following FFP	Reported cases of low and high inhibitor titer. Anamnestic response following rFVIIa	Reported cases of low and high inhibitor titer. Anamnestic response following FXI concentrate	NR. Anamnestic response following FXIII concentrate
Management	Inhibitor eradication: immunosuppressive agents (steroids, cyclophosphamide) Treatment of bleeding: FFP, platelet concentrates, rFVIIa, immunoadsorption, plasmapheresis	Inhibitor eradication: immunosuppressive agents (steroids, cyclophosphamide, azathioprine, immunoglobulin) Treatment of bleeding: rFVIIa	Inhibitor eradication: immunosuppressive agents (steroids, cyclophosphamide) Treatment of bleeding: FXI concentrate (low inhibitor titer), rFVIIa	Inhibitor eradication: ITI (Malmö protocol) Treatment of bleeding: FXIII concentrate

Abbreviations: FFP, fresh frozen plasma; FV, factor V; FVII, factor VII; FXI, factor XI; FXIII, factor XIII; ITI, immune tolerance induction; NR, not reported; rFVIIa, recombinant activated factor VII.

is more extensively characterized than those of other defects, perhaps due to the relatively high frequency of this defect and small size of the gene.<sup>52</sup> To date, more than 130 mutations distributed throughout all the exons have been described, with a considerable proportion of mutations located on exon 8, which codes for the catalytic domain of FVII.<sup>53–56</sup> Missense mutations are the most frequent (70–80%), splicing-site changes are also well represented, while nonsense mutations and small deletions are rare.<sup>52</sup> The severely deficient cases are either homozygous or double heterozygous for mutations that disrupt expression of the protein (i.e., deletions and insertions), resulting in FVII:C levels usually < 1% of normal. Individuals with a mild/moderate clinical phenotype are homozygous or doubly heterozygous for missense mutations.<sup>53</sup> The identification of FVII deficiency may be based on a prolonged PT with normal aPTT, and diagnosis confirmed by reduced FVII:C by modified one-stage PT-based clotting assay. Measurement of plasma FVII:Ag by immunoassay is necessary to distinguish qualitative from quantitative FVII deficiency.<sup>30</sup>

The severity of symptoms of FVII deficiency is quite variable and reported to be poorly correlated with plasma levels. Some patients with severe deficiency do not bleed after major challenges of hemostasis. However, recent studies highlight that the most severe bleeding symptoms are reported in patients with FVII:C below 10% and that age and bleeding pattern at diagnosis may predict the bleeding tendency in such patients.<sup>49,57,58</sup> Life- or limb-endangering bleeding manifestations are relatively rare, the most frequent symptoms being epistaxis and menorrhagia.<sup>59</sup> The high incidence of central nervous system bleeding (16%) reported by Ragni and colleagues<sup>48</sup> in a series of 75 patients affected by FVII deficiency, was not confirmed by two subsequent studies.<sup>53,60</sup> Thrombotic episodes (particularly venous thrombosis), have also been reported in 3 to 4% of patients with FVII deficiency, particularly in the presence of surgery and replacement treatment; however, spontaneous thrombosis may also occur.<sup>60,61</sup>

Current therapeutic options include fibrinolytic inhibitors, fresh frozen plasma, prothrombin complex concentrates, plasma-derived FVII concentrates and rFVIIa.<sup>30</sup> However, the very short half-life of FVII makes it difficult to use fresh frozen plasma without causing volume overload. Recombinant FVIIa has to be considered the optimal replacement therapy since it can be used at a very low dose (15–30 µg/kg).<sup>62–64</sup>

### Anti-FVII Alloantibodies

Rarely, replacement therapy of severe inherited FVII deficiency is complicated by the occurrence of inhibitors against infused FVII.<sup>30</sup> Thirteen inhibitor cases have been reported so far in eight studies, following use of either plasma-derived or rFVII products.<sup>65–72</sup> In a prospective study of 101 spontaneous or traumatic bleeds occurring in 75 patients with congenital FVII deficiency, two inhibitors were detected in two repeatedly treated patients (one post-plasma-derived FVII, one post-rFVIIa).<sup>67</sup> See and colleagues<sup>72</sup> reported the case of FVII inhibitor development following liver transplantation in a 5-year-old girl with severe congenital FVII deficiency. Interestingly, she was responsive to rFVIIa despite the presence of the inhibitor.<sup>72</sup> Also, successful prophylactic rFVIIa in a patient with inherited

FVII deficiency with inhibitors to FVII was reported by Tokgoz and colleagues,<sup>68</sup> suggesting a possible weak affinity of this alloantibody to rFVIIa. By contrast, Borhany and colleagues<sup>71</sup> reported a FVII inhibitor case who did not respond to rFVIIa therapy despite extensive immunosuppressive (methylprednisolone and cyclophosphamide) treatment. The largest experience is that by Batorova and colleagues on behalf of the STER (Seven Treatment Evaluation Registry) study group,<sup>70</sup> who detected FVII inhibitors in 2.6% (3/115) of patients in the registry. All inhibitors were high responders, and all but one were detected in infants with a severe FVII defect and bleeding phenotype.

## Alloantibodies in Congenital FXI Deficiency

### Characteristics of Congenital FXI Deficiency

FXI is a dimeric serine protease mainly synthesized in the liver and encoded by the 23 kb long *FXI* gene located on chromosome 4.<sup>73</sup> Hereditary FXI deficiency is an autosomal bleeding disorder characterized by reduced levels of FXI in plasma and typically manifests as a prolongation of the aPTT with reduced FXI activity, as determined by one-stage modified aPTT clotting assay.<sup>74–76</sup> The prevalence of severe FXI deficiency is approximately 1:1,000,000, although it has been reported to be much in Ashkenazi Jews.<sup>77</sup> Nearly 200 different mutations affecting the *FXI* gene have been identified so far, missense mutations representing more than 60% of all variants.<sup>30,78</sup> Two mutations are responsible for most cases of FXI deficiency in Ashkenazi Jews, while mutations are more varied in non-Jews.<sup>78,79</sup> The type II Jewish mutation is a stop codon in exon 5, leading to undetectable FXI levels in homozygous individuals. The type III Jewish mutation is a missense mutation in exon 9 that causes a defective secretion of the protein from cells, but some FXI is ultimately produced so that measurable levels of FXI (at ~10%) are present in these patients. Type II/III compound heterozygosity is the commonest cause of severe to moderate FXI deficiency in Ashkenazi Jews.<sup>80</sup>

In comparison with hemophilia A or B, bleeding manifestations in FXI deficiency are much less predictable, even in patients with severe deficiency. Bleeding is not related to FXI plasma levels but rather to the site of injury. Thus, the risk of bleeding is increased when at a site of injury with local high fibrinolytic activity (e.g., oral cavity after dental extraction or tonsillectomy, urogenital tract).<sup>81</sup> Patients with severe FXI deficiency are usually mildly affected and most bleeding manifestations are injury-related. Patients with low but detectable levels of FXI are also surprisingly mild bleeders, so that in these two groups clinical phenotypes are not strikingly different.<sup>82</sup> Women with FXI deficiency are prone to excessive bleeding during menstruation, but case series of women affected by severe FXI deficiency showed that 70% of pregnancies were uneventful, despite no prophylactic treatment.<sup>83,84</sup>

Treatment of congenital FXI deficiency is based upon the use of antifibrinolytic agents, fresh-frozen plasma, plasma-derived FXI concentrate and rFVIIa, but attention should be paid to reduce the risk of thrombotic complications (especially when FXI concentrates are employed), volume overload when



fresh frozen plasma is used, and allergic reactions and development of inhibitors following FXI replacement therapy (see below).<sup>73</sup> As surgery or trauma can be associated with excessive and prolonged bleeding unless adequately treated, a careful evaluation of patients with severe FXI deficiency is recommended prior to surgery, as well as meticulous planning of the procedure and of the post-surgical course. FXI has a relatively long half-life (40–70 hours), so that the infusion of 15 to 20 mL/kg virus-inactivated fresh frozen plasma on alternate days should be sufficient to keep FIX at trough hemostatic levels of 15 to 20%.<sup>85</sup>

### Anti-FXI Alloantibodies

A severe complication of replacement therapy in congenital FXI deficiency is the development of inhibitor to infused FXI.<sup>86,87</sup> In a study conducted in 2003 by Salomon and colleagues on 188 Israeli patients with severe FXI deficiency, 7 of 21 patients (33%) homozygous for type II mutation developed inhibitors after exposure to plasma.<sup>88</sup> Characterization of these inhibitors revealed that they were all IgG alloantibodies and inhibited activation of FXI by thrombin or activated factor XII (FXIIa) and inhibited activation of FIX by exogenous FXIa.<sup>88</sup> Patients with FXI deficiency do not bleed spontaneously. Nevertheless, FXI inhibitors may increase surgical- or trauma-related bleeding and reduce responses to FXI replacement.<sup>86</sup> Thus, the presence of an inhibitor should be suspected (and investigated) when replacement therapy with fresh frozen plasma or FXI concentrate fails to correct a prolonged aPTT or when a patient continues to bleed despite appropriate treatment. In such cases, aPTT mixing studies and the modified Bethesda assay are helpful to detect and quantify the FXI inhibitor.<sup>88</sup> In addition, a periodical screening for inhibitor is mandatory in patients with severe FXI deficiency due to null mutations, especially if a surgical procedure is planned.<sup>30</sup>

Pertaining to the treatment of inhibitor patients, when the titer of inhibitor is low, the use of FXI concentrate may be hemostatically sufficient, although an anamnestic response is to be expected.<sup>75</sup> Since the first successful report by Hedner and colleagues in 1990,<sup>89</sup> several authors have reported effective hemostatic treatment of severe FXI deficiency and inhibitors using rFVIIa at doses varying between 30 and 90 µg/kg.<sup>90–93</sup> More recently, Livnat and colleagues<sup>94</sup> observed that relatively low concentrations of rFVIIa corrected in vitro thrombin generation in plasma from patients with severe FXI deficiency and an inhibitor. On the basis of this finding, the same authors treated three patients with severe FXI deficiency and FXI inhibitors who underwent major surgery with a single low dose of rFVIIa (15–30 µg/kg) and tranexamic acid and this protocol secured normal hemostasis without thrombotic adverse events.<sup>95</sup> All in all, these data suggest that rFVIIa in patients with severe FXI deficiency and inhibitors may induce effective hemostasis at doses that are lower than those required for patients with severe hemophilia A or B and inhibitors.<sup>96</sup> Finally, successful inhibitor eradication with immunosuppressive therapy (cyclophosphamide and steroids) has been reported by Teruya and Styler.<sup>97</sup>

## Alloantibodies in Congenital FXIII Deficiency

### Characteristics of Congenital FXIII Deficiency

FXIII, also called fibrin-stabilizing factor, is the last enzyme to be activated in the blood coagulation pathway and functions to crosslink  $\alpha$ - and  $\gamma$ -fibrin chains, resulting in a stronger clot with an increased resistance to fibrinolysis.<sup>98,99</sup> The plasma factor consists of two catalytic A subunits (FXIII-A) and two carrier B subunits (FXIII-B). FXIII-A is synthesized in cells of bone marrow origin, while FXIII-B is produced in the liver. The corresponding genes are located on chromosome 6 and 1.<sup>100,101</sup> Inherited FXIII deficiency is an autosomal recessive disorder with a frequency of approximately 1:2,000,000 in the general population. Routine coagulation screening tests (PT, aPTT and platelet count) are usually normal, and traditionally the diagnosis of FXIII deficiency has been established by the demonstration of increased clot solubility in a 5 M urea or 1% monochloroacetic acid solution. However, such assays may not reliably identify FXIII-deficient patients, and functional or specific immunoassay tests that measure FXIII-A and FXIII-B antigen levels have been developed.<sup>100,102</sup> More than one hundred different mutations have been identified so far in the FXIII registry database (available at: <http://www.f13-database.de>, accessed March 7, 2017), with missense mutations being those most commonly reported for both genes, although the majority of such defects are identified in the A-subunit, scattered throughout the *F13A* gene.<sup>101</sup> Patients with severe disease characterized by low plasma levels of FXIII can have homozygous mutations or compound heterozygous mutations.<sup>103</sup>

Individuals with FXIII deficiency have an increased tendency to bleed.<sup>104</sup> Animal models of severe FXIII deficiency present with intrathoracic, intraperitoneal and subcutaneous hemorrhage.<sup>105</sup> In humans, bleeding from the umbilical stump in the first few days of life is common. Intracranial hemorrhage, ecchymoses, hematomas and prolonged bleeding following trauma are also characteristic.<sup>106</sup> Delayed wound healing was reported in approximately 30% of FXIII-deficient patients, while hemarthroses and bleeding into the muscles are less common than in hemophiliacs.<sup>107</sup> In a study using the largest group of patients with severe FXIII deficiency (93 Iranians) the most frequent mucosal tract bleeding symptom was bleeding in the oral cavity (lips, tongue, gum) followed by menorrhagia and epistaxis.<sup>106</sup> Twenty percent of patients in the reproductive age had intraperitoneal bleeding at the time of ovulation, while 50% of pregnant women had at least one miscarriage.<sup>106</sup>

The clinical severity of FXIII deficiency prompts regular prophylaxis.<sup>98</sup> This mode of treatment is facilitated by hemostatic levels of FXIII as low as 2 to 5%; given the very long plasma half-life of infused FXIII (11–14 days), replacement material can be infused at large intervals (20–30 days).<sup>108</sup> During pregnancies, monthly prophylactic infusions of FXIII concentrate are necessary to prevent abortions. There are two types of FXIII-containing products: a plasma-derived FXIII concentrate and a recombinant FXIII-A<sub>2</sub> product.<sup>108,109</sup> While the former is appropriate for patients with either A or B subunit deficiency, the recombinant FXIII-A<sub>2</sub> concentrate (which contains only the FXIII-A subunit) is only suitable for patients with

FXIII-A subunit deficiency; however, this reflects the majority of such cases of this congenital bleeding disorder.<sup>110–112</sup>

### Anti-FXIII Alloantibodies

Besides severe acquired FXIII deficiency caused by an autoantibody against either of the FXIII subunits,<sup>100</sup> an anti-FXIII antibody may also develop in patients with inherited FXIII deficiency under replacement therapy. The incidence of such alloantibodies is unknown, although it seems to be a very rare event. Indeed, only seven cases of anti-FXIII-A alloantibodies have been reported so far in the literature,<sup>113–119</sup> while there is only a single report on anti-FXIII-B alloantibodies.<sup>120</sup> The most recent report was that published by Penzes and colleagues in 2016.<sup>119</sup> The investigators characterized the anti-FXIII-A alloantibody, isolated from a patient with a severe FXIII-A deficiency and bleeding phenotype, demonstrating that it belonged to IgG class and exerted a multiple inhibitory effect on FXIII activation (interference with thrombin and Ca<sup>2+</sup>-induced FXIII activation) and activity (interference with the transglutaminase activity of activated FXIII).<sup>119</sup> Also, the alloantibody was responsible for an accelerated clearance of administered plasma-derived FXIII concentrate from the circulation. Attempts to eliminate the alloantibody through ITI treatment (Malmö protocol including cyclophosphamide, IVIG, and high-dose FXIII) resulted only in a transient improvement, and the patients died due to intracerebral hemorrhage.<sup>119</sup> Wada and colleagues<sup>120</sup> reported the case of a patient with severe congenital FXIII-B deficiency, whose mild bleeding phenotype was aggravated by the development of an anti-FXIII-B alloantibody. Finally, in a multicenter phase III trial in 41 patients with congenital FXIII-A subunit deficiency treated with recombinant FXIII-A<sub>2</sub> product, 4 patients developed transient, non-neutralizing, low-titer anti-FXIII antibodies.<sup>121</sup>

### Conclusion

The development of inhibitory alloantibodies following replacement therapy in patients with inherited rare bleeding disorders is a very unusual adverse event, occurring much less frequently than reported in patients with congenital severe hemophilia A treated with FVIII concentrates, or even those with congenital severe hemophilia B treated with FIX concentrates. Nevertheless, the management of such rare inhibitors is perhaps even more challenging for caregivers of HTCs, especially considering that the published experience upon which to base their clinical practice is scanty. In this regard, while very little is known about treatments aiming to eliminate these inhibitors, rFVIIa seems to be the most universally acceptable therapeutic option for managing bleeding (except for FXIII deficiency, – **Table 1**). The implementation of international registries aimed at recording additional inhibitor cases and improving our knowledge on their management is greatly welcomed.

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