Treatment of rare factor deficiencies in 2016

Flora Peyvandi and Marzia Menegatti

Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

Rare bleeding disorders (RBDs) are a heterogeneous group of coagulation disorders characterized by fibrinogen, prothrombin, factors V, VII, X, XI, or XIII (FV, FVII, FX, FXI, or FXIII, respectively), and the combined factor V + VIII and vitamin K–dependent proteins deficiencies, representing roughly 5% of all bleeding disorders. They are usually transmitted as autosomal, recessive disorders, and the prevalence of the severe forms could range from 1 case in 500 000 for FVII up to 1 in 2-3 million for FXIII in the general population. Patients affected with RBDs may present a wide range of clinical symptoms, varying from mucocutaneous bleeding, common to all types of RBDs to the most life-threatening symptoms such as central nervous system and gastrointestinal bleeding. Treatment of these disorders is mainly based on the replacement of the deficient factor, using specific plasma-derived or recombinant products. In countries where these facilities are not available, bleedings could be managed using cryoprecipitate, fresh frozen plasma (FFP), or virus-inactivated plasma. Minor bleedings could be managed using antifibrinolytic agents. Recently, 2 novel drugs, recombinant FXIIIA and a plasma-derived FX, have been added to the list of available specific hemostatic factors; only prothrombin and FV deficiencies still remain without a specific product. Novel no-replacement therapies, such as monoclonal antibody anti–tissue factor pathway inhibitor, RNA interference, and a bispecific antibody that is an FVIIIa mimetic, enhancing thrombin generation through different mechanisms, were developed for patients with hemophilia and may in the future be a good therapeutic option also in RBDs.

Learning Objectives

- Rare bleeding disorders are a heterogeneous group of coagulation factor deficiencies with various clinical symptoms
- Management of RBDs is mainly based on expert consensus rather than evidence-based guidelines
- Replacement therapies are differently available for patients affected with RBDs and could range from only FFP to treat FV deficiency to 2 recombinant products (recombinant activated FVII and recombinant FXIII A subunit) available for FVII and FXIII-A deficiencies
- Novel no-replacement therapeutic approaches as anti-TFPI, RNA interference, and bispecific antibodies could be an interesting approach for prophylaxis to prevent bleeding also in patients affected with RBDs, once their safety and efficacy have been proven by proper clinical trials

Introduction

Inherited deficiencies of coagulation plasma proteins generally lead to lifelong bleeding disorders. Hemophilias A and B and von Willebrand factor disease represent together ~95% to 97% of all these deficiencies. The remaining disorders, called rare bleeding disorders (RBDs), are due to the deficiency of fibrinogen, prothrombin (factor II), factors V, VII, X, XI, or XIII (FV, FVII, FX, FXI, or FXIII, respectively), or the combined deficiency of FV + FVIII or vitamin K–dependent proteins.[1] The prevalence of homozygous or double heterozygous forms ranges from ~1 case in 500 000 for FVII deficiency to 1 in 2 to 3 million for prothrombin and FXIII deficiency.[2] Patients affected with these type of disorders can present a heterogeneous spectrum of symptoms that vary from mild or moderate bleeding to potentially serious or life-threatening hemorrhages. The most typical symptoms, common to all RBDs, are mucosal tract bleeding and bleeding at the time of invasive procedures or surgery. Endangering and serious symptoms, as umbilical cord and central nervous system (CNS) bleeding, occur with higher frequency in patients with severe deficiency of fibrinogen, FVII, and FXIII.[3] Gastrointestinal bleeding and recurrent hematomas and hemarthroses are more frequent in FX deficiency.

Due to the rarity of RBDs and the consequent absence of randomized controlled studies, recommendations are mainly based on expert consensus rather than on evidence-based guidelines.[4] On the whole, management of bleeding depends on severity of disease, type of bleeding episode, and minimal residual activity in patients' plasma. The development of guidelines for the classification of RBDs has been historically hampered by the lack of sufficient knowledge about epidemiology and clinical outcome.[5] Classification of the severity of RBDs based on the residual level of the missing factor relied on extrapolations from other bleeding disorders like hemophilia (activity $<1\%$ for the severe form, 1-5% for the moderate, and $>5\%$ for

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the mild), which can have a totally different disease course. In 2007, the European network of rare bleeding disorders (EN-RBD), an initiative started by the university of Milan, Italy, explored the association between residual clotting levels and clinical bleeding severity.[6] This 3-year project, funded by the European Commission, was carried out in 489 patients involving 13 European treatment centers from 11 countries. The results of this study showed a strong association between residual coagulant activity and clinical bleeding severity in fibrinogen, combined FV + VIII, FX, and FXIII deficiencies, a weak association for FV and FVII deficiencies, and no association between FXI residual plasmatic activity level and patients' bleedings history. On the whole, this report confirmed that RBDs are a very heterogeneous group of disorders and could not be considered as a single entity, and the clotting levels necessary to ensure complete absence of major spontaneous bleeding could differ in each RBD.[6]

With this background, in this review article, we describe the current available treatment of RBDs, providing therapeutic target levels for on demand and prophylactic treatment, as well as for minor and major surgeries (Tables 1 and 2). Treatment mainstay, until now, was based on the replacement of the deficient coagulation factor and use of adjunctive therapies including antifibrinolytics and estrogen/progestogen, where appropriate. On the whole, while prescribing a replacement therapy, a hierarchy should be followed based on the safety of replacement products with regard to blood-borne pathogens: specific concentrates including recombinant or plasma-derived products should be considered the first choice for treatment, when available, followed by prothrombin complex and cryoprecipitate. As a last choice, in the absence of any specific product, due to a potential risk of volume overload, other blood products such as virus-inactivated fresh frozen plasma (FFP) may be used.

Fibrinogen deficiency

Fibrinogen disorders may be either quantitative, defined by a complete absence (afibrinogenemia) or decreased antigen and coagulant activity level (hypofibrinogenemia) of circulating fibrinogen, or qualitative, characterized by a discrepancy between fibrinogen antigen and activity. Patients with a qualitative disorder can present with normal (dysfibrinogenemia) or decreased (hypodysfibrinogenemia) antigen levels. Among patients with fibrinogen disorders, afibrinogenemic patients, with both undetectable antigen and activity levels, show the most severe clinical symptoms; the most common are mucocutaneous bleeding, soft tissue and joint bleeding, and prolonged bleeding from the umbilical stump. Some of these patients, with the most severe symptoms, could benefit from long-term prophylaxis[7]; however, the risk of developing thrombotic episodes makes it difficult to adopt a unique and standardized therapeutic strategy in all patients. Patients affected with hypo- or dys-fibrinogenemia, with measurable antigen and activity levels, may show mild bleeding symptoms or remain completely asymptomatic during their entire life.[7] Due to this heterogeneity, any considered treatment should therefore be tailored to the personal and familial history. Among RBDs, fibrinogen deficiency benefits from different specific available concentrates. There are a few available plasma-derived fibrinogen concentrates effective for both on-demand and prophylactic therapy. According to the results obtained from the EN-RBD project, the trough level thus far recommended (0.5-1 g/L) should be moved to an upper limit of 1 to 1.5 g/L (Table 1), which seems to be associated to an asymptomatic status. This level should also be considered in women during pregnancy to prevent miscarriage. Despite the good availability of treatment products, 4 new plasma-derived concentrates have been developed, and for one of them, results from clinical studies suggested the use of 1.2 g/L for major bleeding/surgery and 1.0 g/L for minor bleeding/surgery.[7]

Prothrombin deficiency

Prothrombin deficiency is among the rarest of all bleeding disorders, occurring in ~1 case in 1 to 3 million. Two phenotypes can be distinguished: hypoprothrombinemia, characterized by concomitantly low antigen and coagulant activity levels of the protein; and dysprothrombinemia, characterized by a normal or near-normal antigen level of a dysfunctional protein.[8] Total deficiency of prothrombin appears to be incompatible with life, as demonstrated by the partial embryonic and neonatal mortality in the knockout mouse model.[9] Patients with <5% prothrombin coagulant activity are considered severe and may present with prolonged postinjury bleeding, mucosal bleeding, hematomas, and hemarthroses, whereas patients with higher levels or dys-prothrombinemia may remain asymptomatic. The EN-RBD study collected data on 6 patients with prothrombin deficiency and was underpowered to make any conclusion; however, the EN-RBD data together with those from 3 other national registries (United Kingdom Haemophilia Centre Doctors' Organization registry, the North American Rare Bleeding Disorders Registry, and the Indian registry) identified 10% prothrombin activity as the minimum level to ensure an adequate hemostasis.[10]

There is no single prothrombin concentrate available yet in the international market, making prothrombin complex concentrates (PCCs) and FFP the mainstay of on-demand therapy and long-term prophylaxis (Table 1). For mild bleeding episodes, antifibrinolytic agents could be used.

FV deficiency and combined FV and FVIII deficiency

FV deficiency and combined FV and FVIII (F5F8D) are 2 distinct deficiencies; the former is caused by genetic variants on the *F5* gene, whereas the latter is due to genetic variants on lectin mannose binding protein or multiple coagulation factor deficiency 2 genes (*LMAN1* or *MCFD2*), both encoding proteins involved in the intracellular transport of FV and FVIII.[11] About 75% of patients with FV deficiency have a concomitant low level of FV coagulant activity and antigen (type I deficiency); however, ~25% of them have normal antigen levels (type II deficiency). Patients affected with FV deficiency develop bleeding symptoms within the first 6 years of life; frequent symptoms are epistaxis and menorrhagia, as well as postoperative and oral cavity hemorrhages. In patients with low FV coagulant activity level umbilical stump bleeding, muscle hematoma and hemarthroses have also been reported.[11]

F5F8D is characterized by concomitantly low levels (usually between 5% and 20%) of FV and FVIII, both as coagulant activity and antigen levels, and is associated with a mild to moderate bleeding tendency. The concomitant presence of 2 coagulation defects does not enhance the hemorrhagic tendency that was observed in each defect separately.

No FV concentrate is yet available on the market, and other multifactor concentrates such as PCCs and cryoprecipitate do not contain substantial quantities of FV to be effective. Therefore, current treatment of patients with FV deficiency is accomplished only by administering FFP. In addition to FFP, because platelets contain FV, platelet transfusions have also been used; however, particular attention should be paid on alloimmunization.[12] The EN-RBD study identified that 10% FV is the minimum level to ensure FV-deficient patients remain asymptomatic (Table 1). In F5F8D, bleeding episodes are usually treated on demand and do not require regular prophylaxis;

Table 1. Doses and therapeutic target levels for each RBD on on-demand and prophylaxis

Deficient factor	Plasma half-life	Recommended trough levels		On-demand dosages[4]	Long-term prophylaxis dosages[4]
		Previously reported	After EN-RBD results[6]		
Fibrinogen	2-4 days	0.5-1 g/L	1 g/L	Cryoprecipitate (15-20 mL/kg) Virus-inactivated plasma FFP (15-30 mL/kg) Fibrinogen concentrate (50-100 mg/kg)	Cryoprecipitate: 1 bag every 10 kg every 7-10 days Fibrinogen concentrate: 20-30 mg/kg per week adjusted to maintain trough fibrinogen level*
Prothrombin	3-4 days	20-30%	>10%	Virus-inactivated plasma FFP (15-25 mL/kg) PCC (20-40 U/kg)	PCC: 20-40 U/kg once a week
FV	36 hours	10-20%	10%	Virus-inactivated plasma FFP (15-25 mL/kg) Platelet transfusions could be considered, with particular attention on alloimmunization	Virus-inactivated plasma FFP: 20 mL/kg 2 times/week
FV and FVIII	FV 36 hours FVIII 10-14 hours	10-15%	40%	As for FV + DDAVP for mild FVIII deficiency and pd- or recombinant FVIII concentrates for moderate and severe FVIII deficiency	Usually no need of prophylaxis
FVII	4-6 hours	10-15%	>20%	pd-FVII concentrate (30-40 U/kg) rFVIIa (15-30 μg/kg every 4-6 hours)	Virus-inactivated plasma FFP: 10-15 mL/kg 2 times/week pdFVII: 30-40 U/kg 3 times/week rFVIIa: 20-40 μg/kg 2-3 times/week*
FX[19]	40-60 hours	10-20%	>40%	Virus-inactivated plasma FFP (10-20 mL/kg) PCC (20-30 U/kg) pd-FX/FIX concentrate (10-20 U/kg) pd-FX (25 IU/kg)	PCC: 20-40 units/kg 2 times/week pd-FX/FIX concentrate: 20 U/kg weekly pd-FX: 25 IU weekly
FXI	50 hours	15-20%	—	Virus-inactivated plasma –FFP (15-20 mL/kg) pd-FXI concentrate (15-20 U/kg)	Not indicated
FXIII	9-12 days	2-5%	30%	Cryoprecipitate (2-3 bags) Virus-inactivated plasma –FFP (3-5 mL/kg) pd- FXIII concentrate (20-40 U/kg) rFXIII-A (35 U/kg)	† Cryoprecipitate: 1 bag every 10 kg every 3 weeks pd-FXIII concentrate: 20-40 U or rFXIII-A: 35 U/kg every 4 weeks (in pregnant women interval needs to be shorter: 2-3 weeks)
Vitamin K dependent	Prothrombin, FVII, FIX, FX (see specific factors)			Vitamin K1 10 mg for minor bleeding For severe bleedings: 4-factor PCC 20-30 U/kg or virus-inactivated plasma15-25 mL/kg	Oral vitamin K1 5-20 mg/d In poor responders, consider parenteral vitamin K1 5-20 mg/week

Data on primary prophylaxis are experience of single centers and are not based on specific clinical trials. Grade of evidence is 2B (strength of recommendations are made if clinicians believe that benefits and risks and burdens are finely balanced and quality of evidence is low: further research is very likely to have an important impact) except for FVII and FXI grade 2C (quality of evidence is moderate; further research is likely to have an important impact).
*Prophylaxis needs to be personalized based on patient's clinical and family history.
†Prophylaxis is highly recommended in severe patients.

Table 2. Recommended target trough coagulation factor levels in surgeries

Deficient factor	Maintaining level	Major surgery[4]	Minor surgery[4]
Fibrinogen	>1 g/L until wound healing	Fibrinogen concentrate: 50–100 mg/kg before surgery, daily or every other day infusion in the first 4-6 days and then increase the interval (first 48 hours requires daily evaluation)	
Prothrombin	>20%	PCC: 20-40 IU/kg before surgery with further 10-20 IU/kg every 48 hours (first 48 hours requires daily evaluation)	
FV	>15-20%	Virus-inactivated plasma FFP: 15–25 mL/kg before surgery with further 10 mL/kg every 12 hours, if required Consider additional platelet transfusion if virus-inactivated plasma or FFP is not enough	
FV and FVIII	FV >20% FVIII >50%	Supplement FV replacement as mentioned in Table 1: pd- or rFVIII: 20-40 IU/kg or DDAVP 0.3 μg/kg	
FVII	>20%	rFVIIa: 15–30 μg/kg before surgery and every 4-6 hours, in the first 24 hours, and then increase the interval to 8-12 hours or pd-FVII concentrate: 10-40 IU/kg with similar intervals	For minor surgery, recommendation (2C) suggests to use tranexamic acid 15-20 mg/kg or 1 g 4 times daily or antifibrinolytics If necessary cryo, FFP, or specific missing factor should be considered for 1-3 days, based on type of surgery
FX	>20-30%	PCC: 20-30 IU/kg before surgery with further 10-20 IU/kg every 24 hours, if required Virus-inactivated plasma FFP: 15-25 mL/kg per 24 hours	Each single case should be monitored and other therapeutic approach may be adopted, taken into consideration cardiovascular risk and/or thrombotic history of the patient
FXI	No association between FXI clotting activity level and clinical bleeding severity	Antifibrinolytic agents in patients with no bleeding in previous surgery; pd-FXI concentrate: 10-15 IU/kg. A combination of virus inactivated plasma 15-25 mL/kg and tranexamic acid 15-20 mg/kg or 1 g 4 times daily is an alternative to FXI concentrate	
FXIII	>20%	pd-FXIII concentrate: 10-40 IU/kg per day	
Vitamin K dependent	—	Four-factor PCC (prothrombin, VII, IX, X): 20-30 IU/kg with vitamin K1 5-20 mg; Virus inactivated plasma: 15-25 mL/kg is an alternative if 4-factor PCC is unavailable	

both FV and FVIII sources are needed, therefore, in addition to the use of FFP. 1-Deamino-8-D-arginine vasopressin (DDAVP; for mild FVIII deficiency) or plasma-derived or recombinant FVIII concentrates (for moderate and severe FVIII deficiency) should also be used as on-demand therapy.[4]

A new FV concentrate has recently been developed for clinical use in deficient patients, and preclinical studies are currently being performed for the orphan drug designation application.[13]

FVII deficiency

FVII deficiency is the most common autosomal recessive coagulation disorder, representing about one third of all RBDs.[3] The EN-RBD study showed a weak association between coagulation factor activity level and clinical bleeding severity in 224 patients with FVII deficiency; some patients did not bleed despite very low FVII coagulant activity, whereas others with similar levels had frequent bleedings. Also, patients with partial FVII deficiency may present bleeding episodes as demonstrated by a survey of 499 heterozygous patients, where 19% of them had bleeding symptoms.[14] Overall, the most frequent symptoms were reported to be epistaxis and menorrhagia; more severe bleeding symptoms were hemarthrosis and CNS bleeding, with an incidence of 16% to 18% in a series of 28 patients.[15]

As for other RBDs, the data reported by the EN-RBD study showed that the minimum FVII coagulant level to ensure patients to remain asymptomatic could vary from 10% to 20%.[6] A number of replacement therapeutic options can be offered to patients with FVII deficiency, including FFP, PCCs, plasma-derived FVII concentrates, and recombinant FVIIa (rFVIIa), depending on product availability. rFVIIa is genetically engineered, and it is considered the optimal replacement therapy because of its low dose (15-30 μg/kg). The main limitation of this drug is its short half-life. Therefore, a regular prophylaxis requires ≥2 to 3 infusions per week.[4] To improve the rFVIIa half-life, longer-acting rFVIIa molecules were generated. The first longer-acting FVIIa, a glycoPEGylated rFVIIa (N7-GP), was investigated in 30 healthy volunteers (#NCT01272206) in a phase 1 clinical trial showing that the pharmacokinetics of N7-GP were dose proportional in the range investigated.[16] However, in 1 plasma sample, a positive antibody response against N7-GP and cross-reacting with FVIIa was detected.[16] Later, fusion protein technology[17] was used to generate a rFVIIa molecule fused to albumin (rVIIa-FP) and showed a three to fourfold half-life extension in a phase 1 study in healthy volunteers. Another rFVIIa longer-acting therapeutic protein has also been developed utilizing carboxyl terminal peptide technology and displayed a prolonged hemostatic effect following intravenous and subcutaneous administration in hemophilic animal models. The third longer-acting rFVIIa was generated using the Fc receptor–mediated recycling pathway to protect the FP from catabolism (rFVIIaFc), and based on activity, rFVIIaFc has a 5.5 times longer terminal half-life than rFVIIa in hemophilic mice. None of these molecules, which potentially may improve the treatment of patients with FVII deficiency, particularly for prophylactic therapy, have been used in FVII deficiency yet.

FX deficiency

FX deficiency is one of the most severe RBDs, patients with low coagulant activity levels (<10%) may present severe bleeding symptoms early in life including umbilical stump, CNS, or gastrointestinal bleeding, and commonly they have hemarthroses and hematomas.[6] Common symptoms reported in most patients with the severe form of the deficiency include epistaxis and menorrhagia. Heterozygous patients have been reported with postpartum bleeding requiring treatment.[18] Data from the United Kingdom Haemophilia Centre Doctors' Organization registry demonstrated that the proportion of FX-deficient patients requiring treatment is higher than other RBDs.[4] The EN-RBD study suggested a minimum FX coagulant level for patients to remain asymptomatic might vary from 10% to 20% up to 40% (Table 1), because some heterozygous patients showed bleeding symptoms.[18] The treatment of FX deficiency includes PCC, virus-inactivated products, and a freeze-dried human coagulation FIX/FX concentrate with specified content of both FX and FIX.[19] Recently, a novel, high-purity, high-potency, specifically labeled, plasma-derived FX concentrate has been developed and has received marketing authorization from the European Medicines Agency and the US Food and Drug Administration for the treatment and prophylaxis of bleeding episodes and for perioperative management in patients with hereditary FX deficiency.[20]

FXI deficiency

FXI deficiency is the second most commonly reported RBD, representing 26% of all patients affected with rare coagulation disorders.[3] The incidence of the severe form, defined as FXI coagulant activity level <20%, is very population dependent. In most populations, the prevalence of FXI deficiency is about 1:1 000 000, but it is remarkably higher among Ashkenazi Jews (1:450 individuals).[21] The clinical picture of FXI is very heterogeneous: patients with the severe disorder are at a higher risk of bleeding, but some of them may remain asymptomatic, and patients with partial deficiency may bleed after trauma or surgery. The EN-RBD study did not find any association between FXI clotting activity level and clinical bleeding severity in a group of 133 analyzed patients. Salomon et al reported that it is more likely that in this disorder that the phenotype of bleeding correlates with the site of injury: when a site with high fibrinolysis is involved, the risk of bleeding is increased in comparison with sites without fibrinolysis (1.5-40%).[22] This is also in line with the recent findings by Colucci et al showing a lower clot lysis time in a group of patients with FXI deficiency compared with controls, which may be partially explained by the reduced thrombin-induced thrombin-activatable fibrinolysis inhibitor activation and enhanced activated thrombin-activatable fibrinolysis inhibitor resistance.[23] This could be of great clinical relevance, because the use of antifibrinolytic agents is successful in these patients. However, the entire pathway is not yet clear, and further studies are needed to elucidate the underlying mechanism in these patients. Therefore, current treatment choices are based on antifibrinolytics, virus-inactivated plasma, and plasma-derived FXI concentrate. However, due to the risk of thrombotic events associated with the use of FXI concentrate, management with fibrinolytic agents should be the first choice, whereas FXI concentrate should be limited to the management of patients showing significant bleeding history.[20] rFVIIa has also been used in small dosages for the management of patients undergoing surgery or in patients with inhibitors or having an history of allergy.[21]

FXIII deficiency

Congenital FXIII deficiency is caused by defects in both *FXIIIA* and *FXIIIB* genes; however, the majority of the cases are attributed to genetic variants on the *FXIIIA* gene.[3] The prevalence of FXIIIA deficiency has been estimated at 1 case in 2 to 3 million. The clinical symptoms of FXIII deficiency include delayed wound healing, recurrent spontaneous miscarriage, bleeding of soft and subcutaneous tissue, and life threatening spontaneous CNS bleeding, which is the primary cause of death in affected patients. In cases of severe FXIII deficiency, early manifestation of bleeding from the umbilical cord or

CNS may occur during the neonatal period; therefore, an early primary prophylaxis should be planned immediately after diagnosis.[24] The EN-RBD study found a strong association between clinical severity and clotting plasma levels in a group of 42 patients with FXIII deficiency; it also showed that patients with FXIII coagulant activity levels <30% might bleed with a heterogeneous clinical presentation. In particular, those with low activity levels showed spontaneous major bleeding and spontaneous minor or posttraumatic bleeding.[6] Therefore, a cutoff level of FXIII coagulant activity that could discriminate patients with severe bleeding manifestations from those with minor or no bleeding could be helpful. The recent prospective data collection by the Prospective Rare Bleeding Disorders Database project (www.rbdd.org) followed 64 patients with FXIII deficiency and showed that a level of 15% FXIII clotting activity could be a good therapeutic target to maintain patients with no bleeding.[25] The treatment of FXIII-deficient patients consists of the use of FFP, cryoprecipitate, plasma-derived concentrate, or the recently developed recombinant FXIII for the treatment of patients with FXIII A subunit deficiency (rFXIII-A). The efficacy and safety of the new rFXIII-A was shown in 2012 in a multinational prophylaxis trial demonstrating that a single dose of 35 IU/kg rFXIII-A maintained plasma FXIII levels above 0.1 IU/mL (10%) in patients with FXIIIA deficiency and aged ≥6 years.[26] Complete pharmacokinetics results for younger patients were also recently reported, confirming the same data.[27]

Vitamin K–dependent coagulation factors deficiency

Vitamin K–dependent coagulation factors deficiency is an autosomal recessive disorder caused by mutations in genes encoding enzymes involved in posttranslational modifications and in vitamin K metabolism (γ-glutamylcarboxylase: *GGCX*; vitamin K epoxide reductase: *VKORC*).[28] Vitamin K–dependent coagulation factors deficiency leads to the reduced activities of prothrombin, FVII, FIX, and FX, and it has been reported in <30 families worldwide. This disorder often presents during infancy with severe symptoms such as intracranial hemorrhage or umbilical stump bleeding associated with factor levels <5%. Severely affected children may also present skeletal abnormalities. Treatment is based on oral or parenteral administration of vitamin K that should be started as soon as possible in all patients at diagnosis. However, in patients with no response, 4-factor PCC could be used for acute bleeding episodes or before surgery (Tables 1 and 2) to achieve a rapid increase in clotting factor levels.[4]

Conclusive remarks

Viral inactivation methods and recombinant technology have virtually eliminated the risk of blood-borne infection; however, other potential concentrate-related adverse events persist (eg, thrombosis, hypersensitivity reactions, and rare cases of alloantibodies).[3] Surveillance systems such as the Universal Data Collection by the Centers for Disease Control and Prevention in the United States[29] and the European Haemophilia Safety Surveillance system in Europe[30] register and monitor treatment and its complications. These 2 programs highlight the importance of conducting multinational, multicenter data collection for long-term postregistration surveillance and analyzing large numbers of homogeneous/standardized data to overcome the rarity of these disorders.

In addition, the recent development of novel hemostatic drugs for hemophilia patients may have a revolutionary role in the treatment of patients affected with RBDs. Novel drugs such as anti–tissue factor pathway inhibitor monoclonal antibody and RNA interference are able to downregulate or inhibit the activity of natural anticoagulants as tissue factor pathway inhibitor and antithrombin III and increase thrombin generation.[31,32] Another approach is the use of a bispecific antibody (ACE910) that promotes thrombin generation by binding to FIXa and FX, mimicking the cofactor activity of FVIII. A weekly or monthly subcutaneous infusion of such drugs, proven to be effective in hemophilia,[33,34] also target them as a potential tool for prophylaxis in some RBDs in the future.

Correspondence

Flora Peyvandi, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Via Pace 9, 20122 Milan, Italy; e-mail: flora.peyvandi@unimi.it.

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