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NEW THERAPEUTICS FOR INHERITED AND ACQUIRED BLEEDING CONDITIONS

Treatment of rare factor deficiencies other than hemophilia

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The deficiency of fibrinogen, prothrombin, factor V (FV), FVII, FVIII, FIX, FX, FXI, and FXIII, called rare coagulation disorders (RCDs), may result in coagulopathies leading to spontaneous or posttrauma and postsurgery hemorrhages. RCDs are characterized by a wide variety of symptoms, from mild to severe, which can vary significantly from 1 disease to another and from 1 patient to another. The most typical symptoms of all RCDs are mucosal bleedings and bleeding at the time of invasive procedures, whereas other life-threatening symptoms such as central nervous system bleeding and hemarthroses are mostly present only in some deficiencies (afibrinogenemia, FX, and FXIII). At variance with hemophilia A and B and von Willebrand disease, RCDs are much less prevalent, ranging from 1 case in 500 000 to 1 in 2 million in the general population. Their clinical heterogeneity associated with the low number of patients has led to a delay in the development of appropriate therapies. Indeed, a similar heterogeneity can also be found in the treatment products available, ranging from the specific recombinant proteins to treat FVII- and FXIII-deficient patients to the complete absence of specific products to treat patients with FII or FV deficiencies, for whom prothrombin complex concentrates or fresh frozen plasma are, to date, the only option. The recent development of novel hemostatic approaches for hemophilia, such as the use of nonsubstitutive therapy as RNA interference, anti–tissue factor pathway inhibitor, and the gene therapy aimed at improving the patient's quality of life may also have an important role in the treatment of patients with RCDs in the future. (*Blood*. 2019;133(5):415-424)

Introduction

Hemostasis is a finely tuned balance between procoagulant and anticoagulant forces aimed at the maintenance of a constant blood flow associated with the capacity to rapidly clot to prevent blood loss. If there is blood loss, an unstable primary platelet plug is formed.[1] Its stabilization requires fibrin, which is generated by a complex series of cascade reactions involving different coagulation factors: fibrinogen (factor I [FI]), prothrombin (FII), and FV, FVII, FVIII, FIX, FX, FXI, and FXIII.[2] The deficiency of any of the above-mentioned coagulation factors may result in a coagulopathy leading to either spontaneous or posttrauma and postsurgery hemorrhages. Deficiencies of FVIII and FIX, also known as hemophilia A and B, are the most common, with a prevalence of 1 case in 5000 and 1 in 30 000 males, respectively; together with von Willebrand disease, they account for 95% to 97% of all coagulopathies.[3] At variance, remaining deficiencies, called rare coagulation disorders (RCDs), are much less prevalent, with rates ranging from 1 in 2 million for FII and FXIII deficiencies to 1 in 500 000 for FVII deficiency in the general population.[4] However, taken all together, RCDs represent an important challenge for the clinician, especially in countries where consanguineous marriage is frequent and where they may reach frequencies similar to those of hemophilia B.

RCDs are characterized by a wide variety of symptoms from mild to severe, which can vary significantly from 1 disorder to another and from 1 patient to another. On the whole, the most typical symptoms of all RCDs are mucosal tract bleedings and excessive bleeding at the time of invasive procedures, delivery in women, and circumcision in boys, whereas other life- and limb-endangering symptoms such as central nervous system (CNS) bleeding and hemarthroses are mostly present only in afibrinogenemia and FX and FXIII deficiency.[5] This clinical heterogeneity associated with a lower number of patients affected with RCDs compared with hemophilic patients led, in the past, to a lack of studies aimed at understanding how to recognize and diagnose an RCD. In turn, this lack of knowledge caused a delay in the design and production of adequate therapeutic treatments. This was well witnessed by data collected in the UK national register of bleeding disorders back in 1995. The authors stated that the presentation and management of hemophilia A and B were well described at the time, whereas a number of other less common coagulation factor deficiencies needed attention to help hematologists in planning clinical management and usefully contributing to genetic counseling for the family at risk.[6] In the same year, although recombinant FVIII (rFVIII) was already available for the treatment of hemophilia A and rFIX was genetically engineered and scheduled to enter clinical trials for the treatment of hemophilia B, Cohen and Kessler reported fresh frozen plasma (FFP) as the only available option to treat all RCDs (excepted FXI deficiency, for which a compassionate investigational drug program via the British government made FXI concentrate available in the United Kingdom).[7] To date, things have not changed much, at least for RCDs. Now, different advanced therapies have become a reality for the treatment of hemophilia A and B, whereas for some rare

deficiencies (FII and FV), even a specific concentrate is not yet available.[3]

With this background, in the first part of this manuscript, the current available treatments for RCDs are described. Then, current recommendations on therapeutic target levels for on-demand and prophylactic treatment of each type of coagulation factor deficiency are provided.

Available treatments

The treatment mainstay of RCDs is based on the replacement of the deficient coagulation factor and the use of adjunctive therapies when bleedings are minor or mucosal.

Nonreplacement therapies

Adjunctive therapies, such as antifibrinolytic drugs and hormones, are usually considered for less severe mucosal tract hemorrhage or heavy menstrual bleeding, but may be of particular importance because they may lessen the amount of treatment product required when clotting factor concentrates are limited or not available at all.[8,9]

ε-Aminocaproic and tranexamic acid ε-Aminocaproic (EACA) and tranexamic acid (TA) were identified between the late 1950s and the early 1960s. Both block the lysine-binding sites on the plasminogen molecules, thus reducing affinity of plasminogen to fibrin and resulting in an antifibrinolytic action. TA was found to be ~10 times more effective than EACA and more tolerable, therefore, it has completely replaced EACA.[9] TA can be used either orally or topically, for menorrhagia, nosebleeds, bleeding from the gums, and presurgery; in surgery, its use may reduce the need for factor concentrates. Regarding heavy menstrual bleeding, different agencies give different recommendations, however, the maximum daily dose should not exceed 4 to 6 g.[9] A TA with a new formulation and extended half-life is commercially also available and it seems to be effective at lower and less frequent doses.[9] TA is excreted in the urine, therefore its use is contraindicated in renal tract bleeding[10] and should be used with caution in association with prothrombin complex concentrates (PCCs) or FXI concentrate due to the risk of thrombosis.[11-13]

Combined oral contraceptives, progestogens, and LNG-IUS Combined oral contraceptives, progestogens, and a levonorgestrel-releasing intrauterine device (LNG-IUS), an alternative to TA, are successfully used to reduce menstrual blood loss in women with RCDs despite no formal randomized studies to test the efficacy of oral contraceptives having been performed.[14] Oral progestogen seems to be less effective and less acceptable by women when compared with LNG-IUS in the general population in the short-term.[15] However, the latter device has only been evaluated in a few women with RCDs with menorrhagia who did not respond to medical treatment.[16] In addition, women with RCDs could potentially be at risk of bleeding at the time of insertion; therefore, adequate hemostatic coverage is recommended.[16]

Vitamin K Vitamin K is the treatment of choice to restore coagulation factor activities in patients with vitamin K–dependent coagulation factor deficiency (VKDCFD) and could be administered either orally or parenterally.[17,18]

Replacement therapy

FFP and cryoprecipitate FFP and cryoprecipitate have been the first replacement products available since the 1950s and 1960s, respectively. FFP is a pool of plasma from donors' blood frozen to −35°C and can be used to replace any single coagulation factor. Cryoprecipitate is made from FFP, which is frozen and repeatedly thawed in a laboratory to produce a source of concentrated clotting factors, including fibrinogen, FVIII, FIX, FXIII, and von Willebrand factor.[19,20] Historically, the risk of transmission of infectious agents via plasma-derived products has always been of great concern to those who treat, in particular after the 1980s, when high percentages of patients became infected with HIV-1 and/or hepatitis C virus (HCV), although with different percentages in countries worldwide (Di Minno et al[21] and Arnold et al[22] and references therein). This risk has reduced dramatically after measures, as donor selection and blood screening have been applied to increase safety. To this end, a solvent-detergent (S/D) viral-inactivation method to produce low-volume FFP and cryoprecipitate (400 mL) in a single-use bag system yet preserving the protein quality and integrity has been described.[23] The advantage of FFP is the limited number of donors used to prepare it; however, because of the low starting concentration of factors, a large volume of product may be required to treat a hemorrhage thus leading to the risk of hypervolemia.[24] In conclusion, the use of FFP and cryoprecipitate should be limited to treat patients with congenital factor deficiencies for whom no alternative, specific, and safer therapy is available, and, in this case, a pathogen-inactivated form of cryoprecipitate or FFP is recommended.[25]

PCCs PCCs were firstly introduced in the early 1970s as a source of FIX to treat patients with hemophilia B.[26] These products are eluted from cryoprecipitate-free plasma and are enriched with FII, FVII, FIX, and FX, however, the specific content of each clotting factor, particularly FVII, varies by concentrate.[27] PCCs are therefore available as "4-factor" forms containing FII, FVII, FIX, and FX or as "3-factor" forms, without FVII. In the treatment of FVII deficiency, these concentrates have largely been superseded by high-purity, plasma-derived FVII and rFVIIa. Then, after the advent of specific FX concentrates, PCCs have remained the only product of choice for patients affected by FII deficiency. The major concern regarding their use has been the risk of developing thrombotic complications, therefore, in addition to the coagulation factors, the majority of today's PCCs includes 1 or more coagulation inhibitors such as heparin, antithrombin, and proteins C, S, and Z.[28] As regards viral transmission, the process of PCC production currently includes strict viral inactivation using S/D, pasteurization, nanofiltration, and vapor-heated treatment, which dramatically reduces the risk of pathogen-related infections.[28]

Single-factor plasma-derived concentrates Single-factor plasma-derived concentrates first became available by the early 1970s after laboratory methods for separating FVIII and FIX from pooled plasma were developed.[29,30] Each bottle of product contained an indicated amount of FVIII or FIX. This innovation led to home treatment and allowed more accurate dosing, greatly changing the lives of people with hemophilia. From those years on, specific plasma-derived concentrates were also produced for other clotting factors, and now plasma-derived concentrates are available for fibrinogen, FVII, FX, FXI, and FXIII,[31-35] however, they are only licensed in a few countries.[27]

At variance with FFP, clotting factor concentrates are produced from very large plasma pools (2000 or more donors) and, as already mentioned, during the late 1970s and early 1980s, the pooling of such plasmas, with no virucidal steps, led to the international disaster of thousands of hemophilic patients infected by HIV and HCV. To inactivate infectious particles, virucidal methods were introduced; the transmission of infectious agents via transfusion of blood derivatives occurs very rarely nowadays, at least in resource-rich countries.[36] In 2008, the European Haemophilia Safety Surveillance System (EUHASS) started to monitor the safety of treatments for people with inherited bleeding disorders in Europe.[37] Since then, 2667 adverse events were reported and none were attributable to transfusion-transmitted infections (https://www.euhass.org/). The risk of transmitting hepatitis B virus, HCV, or HIV-1 is minimal; however, non–lipid-enveloped pathogens such as parvovirus B19 could survive the process and be transmissible.[38] Concerns remain regarding the possible transmission of prions by clotting factors, although no documented cases have been reported.[27]

Recombinant coagulation proteins Recombinant coagulation proteins entered into the world of treatments of coagulopathies in the 1990s; in particular, the first commercial rFVIII and rFIX were made available in 1992 and 1997, respectively.[39] In the same years, a rFVIIa protein was also developed and approved in Europe, the United States, and Japan to be used as a bypassing agent in hemophilic patients who developed an inhibitor following treatment with FVIII (or FIX) concentrates.[40,41] Only later was rFVIIa licensed for treatment in patients with FVII deficiency in which it can be used at a lower dose compared with dosing in hemophilic patients with inhibitors.[42] This may be explained by the fact that, at variance with patients with hemophilia, patients with FVII deficiency have an intact FXI-feedback loop ensuring appropriate amplification of initial thrombin generation.[43] The use of rFVIIa in recent years has extended beyond its original indication and has been shown to be a valuable general hemostatic agent in conditions such as trauma, surgery, spontaneous intracerebral hemorrhage, and FXI deficiency.[41,44] The major concern is related to the risks of thrombosis and the development of inhibitory antibodies; however, a low incidence of adverse events has been recently reported in a prospective study carried out on patients with FVII deficiency and over a large array of clinical settings.[45]

The only other recombinant coagulation protein available thus far for the treatment of patients with FXIII A-subunit deficiency is rFXIII-A. Its efficacy and safety have been demonstrated in both adults and children.[46,47] In 2017, Carcao et al reported that 5 of 93 patients with severe FXIII-A subunit deficiency, treated with rFXIII-A (all <18 years of age), have shown transient non-neutralizing antibodies to rFXIII-A2, and no inhibitory antibodies were detected.[48] The use of this recombinant protein was approved in all western countries between 2012 and 2013.

Management of RCDs

Due to the rarity of RCDs and the consequent absence of randomized controlled studies, recommendations are mainly based on expert consensus rather than on evidence-based guidelines.[25] On the whole, management of bleeding depends on severity of disease, type of bleeding episode, and minimal residual activity in patients' plasma. Classification of the severity of RCDs has been historically derived from that of hemophilia (coagulant activity <1%, severe; 1%-5%, moderate; and >5%, mild).[49] However, in 2012, a retrospective study by the European Network of Rare Bleeding Disorders (EN-RBD) exploring the association between residual clotting levels and clinical bleeding severity in 489 patients affected with different RCDs showed that RCDs are a very heterogeneous group of disorders and should not be considered as a single disease and that the clotting levels necessary to ensure complete absence of major spontaneous bleeding is different in each RCD.[50]

In the following part of this review, any single deficiency is briefly described and the current available treatments are reported. Dosages, intervals, and therapeutic levels are reported in Tables 1 and 2; in addition to specific factor treatments, a TA dose of 15 to 20 mg/kg or 1 g 4 times daily should be considered for the treatment of mild bleeding.[25]

Fibrinogen deficiency

Fibrinogen deficiency may be either quantitative or qualitative. Quantitative defects may be caused by the complete absence of the protein (afibrinogenemia) or a concomitant lower antigen and coagulant activity fibrinogen level (hypofibrinogenemia). Qualitative defects are characterized by a discrepancy between fibrinogen activity level and a normal (dysfibrinogenemia) or decreased (hypodysfibrinogenemia) antigen level. Afibrinogenemic patients show the most severe clinical symptoms such as soft-tissue and joint bleeding as well as prolonged bleeding from the umbilical stump in addition to the most common mucocutaneous bleedings. Spontaneous CNS bleedings have been reported as a leading cause of death in some patients[51] who may benefit from a long-term prophylaxis. However, the risk of developing thrombotic episodes makes it difficult to adopt a unique and standardized therapeutic strategy suitable for all. In patients affected with hypofibrinogenemia or dysfibrinogenemia, major bleeds are rarely spontaneous but are more often related to injury, delivery, or surgery whereas thrombosis is a well-established complication. A recent comparison of clinical features in patients with dysfibrinogenemia and hypodysfibrinogenemia suggested that the latter are more prone to develop thrombosis with a high incidence in very young patients. However, family studies did not show a complete segregation of the mutation with the clinical phenotype.[52] Due to this heterogeneity, any considered treatment should therefore be tailored to the personal and familial history. Even though 3 fibrinogen concentrates are already available, the interest in such products is so high that pharma companies, both new and experienced, are developing different new concentrates.[53] In any case, the use of the concentrates should be preferred to cryoprecipitate or FFP because, in addition to avoiding volume overload and preventing risk of infection, more precise dosing can be accomplished with a known potency.

Prothrombin deficiency

Prothrombin deficiency is characterized by either a low production of normal prothrombin (hypoprothrombinemia) or a near-normal production of a dysfunctional protein (dysprothrombinemia).[54] The complete absence of prothrombin seems to be incompatible with life, as demonstrated by the partial embryonic and neonatal mortality in the knockout mouse model.[55] Hypoprothrombinemic patients may present with prolonged post-injury bleeding, mucosal bleeding, hematomas, and hemarthroses, whereas patients with measurable levels of prothrombin >30%/40%

Table 1. Plasma half-life, therapeutic target levels, available treatment, and therapeutic dosages for each RCD (on demand and prophylaxis)

Deficient factor	Plasma half-life	Trough levels		Available treatment	On-demand dosages	Long-term prophylaxis dosages
		Previously reported	EN-RBD*			
Fibrinogen	2-4 d	0.5-1 g/L	1 g/L	Cryoprecipitate	15-20 mL/kg	1 bag/10 kg/7-10 d
				FFP†	15-30 mL/kg	—
				Fibrinogen concentrate	50-100 mg/kg	20-30 mg/kg/wk
Prothrombin	3-4 d	20%-30%	>10%	FFP†	15-25 mL/kg	—
				PCC	20-40 U/kg	20-40 U/kg once/wk
FV	36 h	10%-20%	10%	FFP†	15-25 mL/kg	20 mL/kg 2 times/wk
				Platelet transfusions could be considered, with particular attention on alloimmunization		—
FV and FVIII	FVIII 10-14 h	10%-15%	40%	FV deficiency: (see above) mild FVIII deficiency: DDAVP moderate and severe FVIII deficiency: pd- or rFVIII concentrates		Usually no need for prophylaxis
FVII	4-6 h	10%-15%	>20%	FFP†	—	10-15 mL/kg 2 times/wk
				pd-FVII concentrate	30-40 U/kg	30-40 U/kg 3 times/wk
				rFVIIa	15-30 μg/kg every 4-6 h	20-40 mg/kg 2-3 times/wk
FX	40-60 h	10%-20%	>40%	FFP†	10-20 mL/kg	—
				PCC	20-30 U/kg	20-40 U/kg 2 times/wk
				pd-FX/FIX concentrate	10-20 U/kg	20 U/kg/weekly
				pd-FX	25 U/kg	25 U weekly
FXI	50 h	15%-20%	—	FFP†	15-20 mL/kg	Not indicated
				pd-FXI concentrate	15-20 U/kg	
FXIII	9-12 d	2%-5%	30%	Cryoprecipitate	2-3 bags	1 bag/10 kg/3 wk
				FFP†	3-5 mL/kg	—
				pd-FXIII concentrate	20-40 U/kg	20-40 U/kg/4 wk‡
				rFXIII-A	35 U/kg	35 U/kg/4 wk (2-3 wk in pregnant women)
Vitamin K dependent	Prothrombin, FVII, FIX, FX (see specific factors)			Vitamin K1	10 mg for minor bleeding	5-20 mg/daily (orally) 5-20 mg/wk (parenteral)
				4-factor PCC	20-30 U/kg	—
				FFP†	15-25 mL/kg	—

Plasma half-life, therapeutic target levels, available treatment, and therapeutic dosages for each RCD (on demand and prophylaxis).[12,48]

—, no data; DDAVP, 1-deamino-8-D-arginine vasopressin; EN-RBD, European Network of Rare Bleeding Disorders; pd, plasma derived.

*EN-RBD retrospective study (2007-2010).[48]

†Virus-inactivated plasma preferable.

‡In countries with low income and a high number of patients with FXIII deficiency, a prophylaxis program of 10 U/kg every 4 or 6 wk was shown to be cost-beneficial and acceptable for prevention of severe bleeding symptoms.[95]

Table 2. Recommended target trough levels in major surgeries for different RCDs

Deficient factor	Maintaining level	Minor surgery	Major surgery
Fibrinogen	>1 g/L until wound healing	If necessary cryo, FFP, or specific missing factor should be considered for 1-3 d, based on the type of surgery; the use of TA may reduce the need for factor concentrates: the first dose should be given immediately before starting if IV or 2 h if oral	Fibrinogen concentrate: 50-100 mg/kg before surgery, daily, or every-other-day infusion in the first 4-6 d, then increase the interval (first 48 h requires daily evaluation; it is important not to exceed)
Prothrombin	>20%		PCC: 20-40 IU/kg before surgery with further 10-20 IU/kg/48 h (monitoring of coagulation is required in the first 48 h)
FV	>15%-20%		FFP*: 15-25 mL/kg before surgery with further 10 mL/kg/12 h, if required (monitoring of coagulation is required in the first 48 h)
FV and FVIII	FV > 20% FVIII > 50%		FV replacement as mentioned in Table 1 pd or rFVIII: 20-40 IU/kg or DDAVP 0.3 mg/kg
FVII	>20%		rFVIIa: 15-30 mg/kg before surgery and every 4-6 h, in the first 24 h, then increase the interval to 8-12 h or pd-FVII concentrate: 10-40 IU/kg with similar intervals
FX	>20%-30%		PCC: 20-30 IU/kg before surgery with further 10-20 IU/kg/24 h, if required or FFP*: 15-25 mL/kg/24 h pd-FX: data on 4 major and 3 minor surgeries were published by Escobar et al[69]
FXI	Not available		Antifibrinolytic agents in patients with no bleeding in previous surgery; pd-FXI concentrate: 10-15 IU/kg; a combination of FFP* 15-25 mL/kg and TA 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/d rFXIII: first data on minor surgery were recently published by Carcao et al[96]
Vitamin K dependent	—		4-factor PCC: 20-30 IU/kg with vitamin K1 5-20 mg or virus-inactivated plasma: 15-25 mL/kg

Recommended target trough levels in major surgeries for different RCDs.[12] Each single case should be monitored and other therapeutic approaches may be adopted, taking into consideration cardiovascular risk and/or thrombotic history of the patient.

—, no data; cryo, cryoprecipitate. Other abbreviations are explained in Table 1.

*Virus-inactivated plasma would be preferable.

or dysprothrombinemia may remain asymptomatic. No specific plasma-derived or recombinant prothrombin products are available, therefore, in severe clinical settings, an adequate level of prothrombin may be achieved with FFP or with PCCs, which avoids the risk of volume overload sometimes associated with the use of FFP. The use of PCCs may be associated with thrombotic risk, in particular in patients requiring prophylaxis, therefore, the evaluation of the antigen level is extremely important to ascertain the type of deficiency.[54] In fact, it has been reported that dysfunctional prothrombin deficiency could be associated with thrombotic disorder.[56]

FV deficiency and combined FV+FVIII deficiency

FV deficiency and combined FV and FVIII deficiency (FV+FVIIID) are 2 distinct deficiencies.

FV deficiency FV deficiency is caused by genetic variants on the *F5* gene. The most frequent symptoms of FV deficiency are epistaxis and menorrhagia, as well as postoperative and oral cavity hemorrhages; in patients with a low FV coagulant activity level, umbilical stump bleeding, muscle hematoma, and hemarthroses have also been reported.[4] As reported in a study, 14% of patients experience spontaneous major bleedings, including CNS hemorrhage, thus requiring prophylaxis[57]; 2 cases were reported to receive an orthotropic liver transplantation as curative treatment of FV deficiency after severe intracranial hemorrhages.[58] The first FV concentrate for clinical use in FV-deficient patients has been recently developed, and it has been shown to correct laboratory parameters (prothrombin time, partial thromboplastin time, and thrombin generation) in severe FV-deficiency plasmas.[59] However, it is not yet commercially available and its outcomes in FV-deficient patients remain to be clarified. PCCs and cryoprecipitate do not contain substantial quantities of FV to be effective. Therefore, the only available treatment of patients with FV deficiency is FFP. Platelet

transfusions could also be used; however, particular attention should be paid on alloimmunization.[60]

FV+FVIIID FV+FVIIID is caused by genetic variants on lectin mannose-binding protein (*LMAN1*) or multiple coagulation factor deficiency genes (*MCFD2*), both encoding proteins involved in the intracellular transport of FV and FVIII.[57] FV+FVIIID is associated with a mild to moderate bleeding tendency, and the concomitant presence of 2 coagulation defects does not enhance the hemorrhagic tendency that was observed in each defect separately.

In FV+FVIIID, bleeding episodes are usually treated on demand and during surgery. Both FV and FVIII sources are needed, therefore, in addition to a FV source, 1-deamino-8-D-arginine vasopressin (DDAVP; for mild FVIII deficiency) or plasma-derived or rFVIII concentrates (for moderate and severe FVIII deficiency) should also be used for the on-demand therapy.[25]

FVII deficiency

FVII deficiency is 1 of the 2 most common inherited coagulation disorders, representing approximately one-third of all RCDs.[4] Its severity ranges from lethal to mild, or even to an asymptomatic disease, often regardless of the coagulant activity level. The most frequent symptoms were reported to be epistaxis and menorrhagia, whereas more severe symptoms were hemarthrosis and CNS bleeding with an incidence of 16% to 18%.[61]

A number of replacement therapeutic options can be offered to patients with FVII deficiency, but rFVIIa is considered the optimal replacement therapy as used at a low dose. Despite its short half-life, a regular prophylaxis of 2 to 3 infusions per week seems to be sufficient.[25,62]

However, to improve rFVIIa half-life, longer-acting rFVIIa molecules were generated by means of fusion technology. Three different new molecules are currently under study: an albumin fused rFVIIa molecule (rVIIa-FP), which showed a threefold to fourfold half-life extension in a phase 1 study in healthy volunteers[63] and has completed a phase 2/3; a C-terminal peptide molecule that displayed a prolonged hemostatic effect following IV and subcutaneous administration in hemophilic animal models[64]; and an Fc receptor–mediated recycling pathway to protect the FP from catabolism (rFVIIaFc) with a 5.5 times longer terminal half-life than rFVIIa in hemophilic mice.[65] However, none of these molecules have yet been used in FVII-deficient patients.

FX deficiency

FX deficiency is 1 of the most severe RCDs, and patients with low coagulant activity levels may present severe bleeding symptoms early in life including umbilical stump, CNS, or gastrointestinal bleeding and commonly may have hemarthroses and hematomas.[4] Postpartum bleeding requiring treatment has also been reported in heterozygous patients.[66] In addition to FFP and PCC, largely used in the past,[67] 2 different concentrates are now available and have facilitated prophylaxis: a freeze-dried FIX/X concentrate with specified FIX/X content and a novel, high-purity, high-potency, specifically labeled, plasma-derived-FX concentrate, which has recently received marketing authorization in both the United States and the European Union.[68-70]

FXI deficiency

FXI deficiency is the other most commonly reported RCD, in addition to FVII deficiency. In most populations, its prevalence is about 1:1 000 000, but it is remarkably higher among Ashkenazi Jews (1:450 individuals) and French Basques.[71] Its clinical picture 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. It has been reported 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.[72] More recently, it has been shown that the resistance to fibrinolysis is reduced in FXI-deficient patients due to different mechanisms, including defective thrombin-activatable fibrinolysis inhibitor (TAFI)-dependent inhibition of fibrinolysis, partly ascribable to unknown activated TAFI resistance. Further studies may help to confirm the clinical usefulness of assaying the TAFI pathway for the evaluation of the bleeding risk.[73] This could be of great clinical relevance because the use of antifibrinolytic agents has been shown to be successful in these patients. Current treatments are based on antifibrinolytics, virus-inactivated plasma, and plasma-derived-FXI concentrate. However, the risk of thrombotic events associated with the use of FXI concentrate has led, over the years, to subsequent revisions of the guidelines regarding both the dosage (from 30 IU/kg to 10-15 IU/kg) and the general recommendation.[74]

Low-dose, off-label rFVIIa has also been used for management in patients undergoing surgery or in patients with inhibitor or having a history of allergy.[71]

FXIII deficiency

Congenital FXIII deficiency is caused by defects in both *F13A* and *F13B* genes; however, the majority of the cases are attributed to genetic variants on the *F13A* gene.[4] The prevalence of FXIIIA deficiency has been estimated at 1 in 2 to 3 million. The clinical symptoms of FXIII deficiency include delayed wound healing, recurrent miscarriage, bleeding of soft tissue, and life-threatening spontaneous CNS bleeding, which is the primary cause of death in affected patients. In severe FXIII deficiency, early manifestation of bleeding from the umbilical cord or CNS may occur during the neonatal period, therefore special precautions must be used from the time of delivery[75] and an early primary prophylaxis should be planned immediately after the diagnosis.[76] Carriers of heterozygous mutations are often asymptomatic and bleed almost exclusively under special circumstances like surgery or induced trauma thus leading to an underdiagnosed disorder.[77] When FXIII concentrate is not available, cryoprecipitate should be preferred to FFP due to higher FXIII content.[78] Plasma-derived-FXIII concentrate has been used for several years and has been shown to be safe and effective. Now a new rFXIII-A2 concentrate (rFXIII-A2) is available. A recent prospective data collection (PRO-RBDD project) on 64 patients with FXIII deficiency showed that a level of 15% of FXIII-clotting activity could be a good therapeutic target to maintain patients with no bleeding.[79] Previous data, evaluating pharmacokinetics of rFXIII, showed that the trough geometric mean FXIII activity level was 0.16 IU/mL.[80]

VKDCFD

VKDCFD is an autosomal-recessive disorder caused by mutations in genes encoding enzymes involved in posttranslational

Table 3. Recommendations and suggestions for the treatment of women affected with RCDs

Deficiency	Notes	
Afibrinogenemia	High level of fibrinogen is recommended to prevent early fetal loss (>1.0 g/L throughout pregnancy) and placental abruption during labor and to prevent PPH (ideally >2.0 g/L)	In women with a history of thrombotic episodes or other risk factors for venous thrombosis, postpartum management should take into account prophylaxis with low-molecular-weight heparin
Hypofibrinogenemia	Intrapartum replacement is required if the fibrinogen level is <1.5 mg/dL and/or the woman has a significant bleeding history; thrombosis events were reported during the puerperium, hence postpartum management should take into account any personal and family history of bleeding and thrombosis	
Dysfibrinogenemia	Dysfibrinogenemic women are at risk of both postpartum thrombosis and PPH; postpartum management of these women should be individualized based on their fibrinogen level as well as personal and family history of bleeding and thrombosis; women without symptoms should not be treated; data on genetic mutation and family history should also be taken into account	
FII	Limited available data	
FV	Women with low FV levels appear to be at increased risk of PPH, hence replacement therapy with FFP is recommended to raise FV level to >15%-25%	
FV + FVIII	Not enough information on pregnancy in these women; the obstetric experience of women with FV deficiency and carriers of hemophilia could probably serve as a useful guide in these patients: during labor FV levels should be >15% and FVIII levels >50%	
FVII	Women with low FVII levels (<10%-20%) or positive bleeding history are more likely to be at risk of PPH, therefore, prophylactic treatment should be considered	
FX	Patients with severe FX deficiency tend to be the most seriously affected patients with RCDs, therefore, they may benefit from replacement therapy during pregnancy and to cover labor and delivery to minimize the risk of bleeding complications; product containing FX to maintain FX level >30%-40% should be used; a pure specific FX is preferable	
FXI	The lack of correlation between FXI level and bleeding risk makes the management of FXI deficiency in pregnancy difficult; antifibrinolytic agents are effective for the majority of women with FXI deficiency, but those with severe deficiency may require FXI concentrate; rFVIIa has also been used to prevent bleeding, however, all treatments should be used with caution in pregnancy due to thrombogenic potential; the risk of PPH can be minimized by obstetric measures	
FXIII	Successful pregnancy in women with FXIII subunit A deficiency is only achieved with prophylaxis during pregnancy; target FXIII level should be >10%-20% until the week 22 of gestation; at the onset of labor, FXIII level need to be increased to >30% by shortening the therapeutic intervals	
Vitamin K dependent	15 mg daily of oral vitamin K and administration of FFP in case of episitomy	

PPH, postpartum hemorrhage.

modifications and in vitamin K metabolism (γ-glutamylcarboxylase [*GGCX*] and vitamin K epoxide reductase [*VKORC*]).[81] VKDCFD leads to the reduced activities of prothrombin, FVII, FIX, and FX, and 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 below 5%. Administration of vitamin K usually resolves the hemostatic problems. For no-responders, PCCs or FFP could also be used; the former should be preferred to avoid volume overload.

Combined inherited coagulation factor deficiencies

These deficiencies are rarely reported and may result from coincidental inheritance of separate coagulation factor deficiencies (due to separated genetic mutations), or from large deletions or chromosomal abnormalities, as in the case of combined FVII+FX deficiency (whose genes are both located on the long arm of chromosome 13).[82-84] Such combined defects often create diagnostic difficulties because results cannot be explained if a single factor deficiency is assumed.

Future therapies

Treatment of RCDs owes much to previous experiences in hemophilic patients, as this review has also shown. Once again, the recent development of novel hemostatic drugs for hemophilia, aimed at increasing safety and improving the patient's quality of life by reducing the number of drug infusions by a higher trough

level, might have an important role in the treatment of patients affected with RCDs.

One novel approach using RNA interference (small-interfering RNA) was explored in patients with severe hemophilia in a phase 1 study that demonstrated that either weekly or monthly subcutaneous administration of ALN-AT3 (Fitusiran) led to a reduction in antithrombin activity associated with an increase in peak thrombin generation.[85] Preliminary studies testing the in vitro effect of ALN-AT3 on the reduction of antithrombin activity in FV-, FVII-, and FXI-deficient plasma samples showed an increase in thrombin generation and the normalization of coagulation parameters.[86]

Another approach is based on anti–tissue factor pathway inhibitor (TFPI) monoclonal antibody, which is able to bind to the Kunitz-type protease inhibitor 2 domain of TFPI thereby blocking the interaction of this domain with the active site of FXa.[87] Currently, 3 interventional phase 1 or 2 clinical trials are investigating different anti-TFPI molecules in patients with either hemophilia A or B, with or without inhibitor (clinicaltrials.gov NCT03196284, NCT03363321, and NCT02571569). It remains to be ascertained whether these molecules could also become a possible therapeutic strategy in RCDs.

Finally, gene therapy, which is having major success in hemophilia A and B, is currently being explored in FVII deficiency. A clinically therapeutic expression of 15% was attained stably for >1 year in an animal model with <1% FVII activity with no evidence of pathological activation of coagulation, detrimental animal physiology, or antibody development.[88] The next step, once the safety of this approach has been assessed, should be its application in the most severe RCDs.

Special consideration in women with RCDs

Women with RCDs are at particular risk of bleeding complications during menstruation, pregnancy, and delivery.[14] Menorrhagia is the most frequent symptom reported in almost half of women with RCDs and can be the first or only presenting symptom, often at menarche. Recurrent miscarriages are frequently described in afibrinogenemic and FXIII-deficient women,[4] and pregnancy and childbirth also pose special clinical challenge with risk of bleeding during pregnancy, delivery, and postpartum. In fact, during pregnancy, even if levels of some coagulation factors may increase, women are not always protected from bleeding, particularly in cases of severe deficiencies.[14,89] Postpartum bleeding often occurs in women with all types of RCDs if replacement therapy is not administered for several days after delivery.[90] On the whole, RCDs can affect women's quality of life because of limitations in activities and work, family and social interactions, and alteration of their reproductive life. The awareness of an underlying bleeding disorder allows for appropriate management,[14] and the ideal management of these women should be through a multidisciplinary clinic including a broad representation of expertise (nurses, clinical hematologists, gynecologists and obstetricians, family physicians, and social workers would be of help). However, at the present time, very few of these clinics are available and they are all located in tertiary care centers.

In Table 3, recommendations and suggestions from available literature for the treatment of women affected with RCDs are reported.[89-94]

Authorship

Contribution: M.M. revised the literature and wrote the text; and F.P. wrote and revised the text.

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Footnote

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