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NEW THERAPEUTICS FOR INHERITED AND ACQUIRED BLEEDING CONDITIONS

New therapies using nonfactor products for patients with hemophilia and inhibitors

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Regular prophylaxis with factor VIII (FVIII) or FIX products to prevent bleeding in patients with severe hemophilia A (HA) and HB, respectively, results in marked suppression of the onset of arthropathy and contributes greatly to improvements in quality of life. Some issues remain with the use of clotting factor replacement therapy, however. The need for multiple IV infusions is associated with a substantial mental and physical burden, and the hemostatic effect of bypassing agents (BPAs) in patients with inhibitor is inconsistent. The development of subcutaneous products with prolonged hemostatic efficiency, irrespective of the presence of inhibitors, has been a longtime wish for patients. A new class of therapeutic agents that act by enhancing coagulation (emicizumab) and inhibiting anticoagulant pathways (fitusiran and concizumab) have been established, and clinical trials using these nonfactor products are ongoing. The current findings have demonstrated that prophylaxis by nonfactor products supports marked reductions of bleeding episodes in hemophilia patients with or without inhibitor. Emicizumab has already been approved for use internationally. Some concerns are evident, however. Thrombotic microangiopathy and thromboembolism have occurred in 5 emicizumab-treated patients receiving repeated infusions of activated prothrombin complex concentrates, and a sinus vein thrombosis has occurred in a fitusiran-treated patient receiving repeated infusions of FVIII product. Moreover, reliable techniques to monitor hemostatic function in patients receiving nonfactor products with concomitant BPA or FVIII/FIX therapies require further assessment. These novel therapeutic agents have promising hemostatic properties, although wider experience in hemophilia centers is warranted to establish appropriate therapeutic strategies. (*Blood*. 2019;133(5):399-406)

Introduction

Hemophilia A (HA) and HB are congenital bleeding disorders caused by quantitative or qualitative abnormalities of coagulation factor VIII (FVIII) and FIX, respectively. Based on baseline levels of procoagulant activity, patients are classified into 3 types.[1] Severely affected patients present with serious hemorrhage from early childhood, and without appropriate treatment, repeated bleeding into joints leads to irreversible chronic arthropathy.[2,3] Advances with treatment, especially regular prophylaxis with FVIII(FIX) concentrates, controls hemarthrosis and results in marked suppression of the onset of arthropathy, contributing greatly to improvements in quality of life.[4,5]

Significant barriers with this type of treatment remain, however, that are categorized as follows: (1) the currently available extended-half-life FVIII(FIX) products reduce the frequency of IV administration, but treatment is still required twice per week (half-life [$t_{1/2}$] ~1.5-fold of FVIII)[6-9] or once per week ($t_{1/2}$ 2.5- to 5-fold of FIX)[10-12]; (2) complications associated with securing venous access, particularly in infants; and (3) the development of anti-FVIII(FIX) neutralizing alloantibodies (inhibitors), affecting 20% to 30% of patients with severe HA and 3% to 5% of those with severe HB.[13,14]

The main treatment of hemophilia patients with inhibitors is on-demand treatment or regular prophylaxis with bypassing agents (BPAs),[15,16] including recombinant FVIIa (rFVIIa), activated prothrombin complex concentrates (aPCC), and plasma-derived FVIIa/FX complex.[17] These protocols have limited success in controlling hemorrhage, however.[18,19] An alternative approach is immune tolerance induction (ITI), an option that aims to eradicate the inhibitors. Several ITI registries indicate that this treatment is successful in 60% to 70% of HA patients and 20% to 30% of HB patients.[20-24] Clinical management is intensive, however, requiring frequent and long-term administration of factor concentrates. Anaphylactic reactions or complications related to nephrotic syndrome are often evident in HB.[25,26]

More effective and less burdensome treatment designed to overcome these unmet needs of current therapeutic strategies would offer considerable advantages for hemophilia patients with or without inhibitors. In this context, some nonfactor therapeutic products have been recently designed with the concept of being long-acting, subcutaneously administered, and effective irrespective of the presence of inhibitors. These novel agents act by enhancing coagulation (emicizumab)[27] or inhibiting anticoagulant pathways (eg, fitusiran, concizumab),[28,29] and initial clinical trials suggest very effective outcomes. Emicizumab (Hemlibra,

Table 1. Comparison with nonfactor products

	Emicizumab	Fitusiran	Concizumab
Manufacturer	Chugai/Roche	Alnylam/Sanoffi	Novo Nordisk
Action mechanism	Bispecific antibody to FIXa/FIX and FX/FXa	siRNA targeting antithrombin	Anti-TFPI antibody
Administration	SC	SC	SC
$t_{1/2}$	28.3-34.4 d	Shorter (plasma), longer (liver)	74.8-114 h
Frequency	QW, Q2W, Q4W	QW, QM	Twice weekly, QD
Target patients	Hemophilia A noninhibitor, inhibitor	Hemophilia A, B noninhibitor, inhibitor	Hemophilia A, B noninhibitor, inhibitor
Risk of ADA	Positive: 1 case (HAVEN 2) and 3 cases (2; SQ, 1; IV, single injection for healthy volunteers)	None	Possible
Complication	TMA (n = 3), TE (n = 2)	TE (n = 1)	No reported
Other	Fatalities with compassionate use/expanded access (unrelated to drug)		
Monitoring	aPTT, chromogenic	Antithrombin level	Free TFPI level
	clot waveform	TGT	TGT
	ROTEM/TEG, TGT		
Ongoing study	Phase 3: noninhibitor	Phase 3	Phase 2
	QW, Q2W, Q4W	QW, QM	daily
	Phase 3: inhibitor		
	Q2W, Q4W		
Approval	HEMLIBRA (inhibitor)	None	None

QW, once weekly; Q2W, every 2 weeks; Q4W, monthly; SC, subcutaneous, siRNA, small interfering RNA; TGT, thrombin generation test.

Hoffman-La Roche/Chugai) has been approved for use internationally. Evidence is encouraging, but caution is necessary at present. Complications of thrombotic microangiopathy (TMA) and thromboembolism in 5 emicizumab-treated patients receiving aPCC and a sinus vein thrombosis in a fitusiran-treated patient receiving FVIII products have been reported.[30,31] A current review focuses on current clinical trial data for nonfactor products that offer the potential for a paradigm shift in hemophilia treatment.

Concepts of nonfactor products

Enhancing coagulation

Emicizumab Emicizumab is a humanized anti-FIXa/FX asymmetric bispecific antibody (human immunoglobulin G_4/κ) that recognizes the epidermal growth factor–like domain 1 of FIX/FIXa with one arm and the epidermal growth factor–like domain 2 of FX/FXa with the other arm (Table 1).[32-34] It functions, therefore, as a FVIIIa cofactor mimetic by binding simultaneously to FIXa and FX and mediating an appropriate structure in the tenase complex. The weak binding affinities minimize unwanted interference up- and downstream of the coagulation cascade and allow the resultant FXa to be released for downstream reactions.[32] The function of emicizumab depends on phospholipids,[27] indicating that emicizumab expresses activity at bleeding sites. Emicizumab has both similarities and dissimilarities to FVIIIa. The functional mechanisms of emicizumab have recently been well reviewed.[33] The antibody was shown to have good pharmacokinetic properties in nonhuman primates, with ~100% subcutaneous bioavailability and a $t_{1/2}$ of 3 to 4 weeks.[35] In a primate-acquired HA model, emicizumab, given as single IV bolus of 1 or 3 mg/kg, controlled artificially induced subcutaneous or muscle bleeds to a similar degree as porcine FVIII administered at twice-daily IV doses of 10 U/kg.[35] Moreover, weekly subcutaneous doses of emicizumab substantially prevented bleeding episodes, including joint bleeding.[36]

Rebalancing coagulation

Normal hemostasis depends on a delicate balance between natural procoagulant and anticoagulant mechanisms.[37] A disturbance in this balance changes the hemostatic status toward either a bleeding or thrombotic tendency. The bleeding phenotype of hemophilia patients is governed by a combination of several factors that influence the natural hemostatic balance,[38,39] and several reports have indicated that plasma proteins commonly associated with inherited thrombophilia, such as genetic defects of antithrombin and protein C/S, impact the clinical features of hemophilia patients.[40-42] On this basis, novel therapeutics that target the natural anticoagulants antithrombin and tissue factor pathway inhibitor (TFPI) have been developed with the aim of rebalancing the hemostatic system in hemophilia.

Fitusiran Antithrombin significantly inactivates FXa and thrombin, and silencing antithrombin causes a clinically hypercoagulable state. Paradoxically, however, an elegant study in a murine HA model indicated that suppression of antithrombin in circulating plasma in these conditions could improve thrombin generation and attenuate the clinically severe bleeding symptoms.[43] No prothrombotic markers were observed, and antithrombin deficiency increased the life span of FVIII-deficient mice.[43] Moderating coagulation gene transcription utilizing the technology of small interfering RNA coupled to *N*-acetylgalactosamine has been proposed for various coagulation proteins.[44,45] The conjugated polypeptides can be administered subcutaneously and target hepatocytes through uptake by the asialoglycoprotein receptor. Consequently, an antithrombin RNA interference agent was developed (ALN-AT3; fitusiran, Alnylam/Sanoffi) to turn off the hepatic expression of antithrombin messenger RNA (Table 1).[46,47] In a preclinical study in animal models, subcutaneous administration of fitusiran demonstrated potent, dose-dependent, and durable reduction of antithrombin levels, restoring hemostasis and improving the coagulation potential of thrombin generation.[43]

Concizumab TFPI is a Kunitz-type proteinase inhibitor that plays an important function in governing tissue factor (TF)–associated procoagulant responses[48] and blocks the initiation of blood coagulation by inhibiting FVIIa-TF and early forms of prothrombinase. A K1 domain of TFPI binds to the active site of FVIIa, a K2 domain binds to the active site of FXa, and a K3 domain interacts with protein S, which is responsible for the cell surface localization of TFPI.[49] Animal studies demonstrated that TFPI inhibition enhanced the hemostatic activities of FVIIa-TF and prothrombinase complexes, resulting in increased clot formation stability and decreased hemophilia bleeding.[50] Platelet-TFPI appeared to be a primary physiological regulator of bleeding in hemophilia,[51] indicating that TFPI inhibition using site-specific antibodies offers an alternative approach for therapeutic management for hemophilia. Aptamer,[52,53] peptide,[54] fucoidan,[55] and monoclonal antibody (mAb)[29] agents have been developed to inhibit TFPI. Concizumab (Novo Nordisk), a humanized mAb against TFPI, seems to have made the clinical advance.[29] It inhibits the K2 domain, thus preventing TFPI-FXa binding (Table 1). Studies in vitro indicated that the regulatory function of TFPI on the TF pathway was moderated, leading to amplified generation of FXa and thrombin.[56] In a rabbit hemophilia model, IV or subcutaneous administration of concizumab significantly reduced cuticle bleeding, with an effect comparable to that of rFVIIa.[29]

Clinical trials in hemophilia patients

Emicizumab

The phase 1 clinical study was conducted in 40 Japanese and 24 white healthy volunteers that received a single subcutaneous dose of up to 1 mg/kg. Emicizumab showed a linear pharmacokinetic (PK) profile and a $t_{1/2}$ of 4 to 5 weeks.[57] A dose-escalation study was performed in 18 Japanese severe HA patients (>12 years of age; 11 inhibitors and 7 noninhibitors) using once-weekly subcutaneous injections of emicizumab at 0.3, 1, and 3 mg/kg for 12 weeks.[58] No serious adverse events (SAEs) were observed. No relevant clinical coagulation abnormalities or thromboembolic events were observed, although FVIII or BPAs were used for breakthrough bleeds. Emicizumab did not affect plasma FIX and FX levels. Median annualized bleeding rates (ABRs) decreased significantly, from 32.5 to 4.4 (0.3 mg/kg), 18.3 to 0.0 (1 mg/kg), and 15.2 to 0.0 (3 mg/kg). No bleeding events were recorded in 8 inhibitor patients or 5 noninhibitor patients. In a phase 1/2 extended study,[59] the longer-term emicizumab treatment (up to 33 months) was well tolerated, with no development of neutralizing anti-emicizumab antibodies (ADAs). Mean steady-state plasma levels of emicizumab increased dose proportionally and were 10.3 (0.3 mg/kg), 29.9 (1 mg/kg), and 120 (3 mg/kg) μg/mL. Median ABRs still remained low at 1.4, 0.2, and 0, respectively. No bleeding events were observed in 8 patients. Dose uptitration resulted in a further reduction of ABRs in patients with insufficient bleeding control. No thromboembolic events were observed in patients requiring concomitant therapy with FVIII or BPAs.

Subsequently, a global phase 3 study was conducted to assess once-weekly subcutaneous emicizumab prophylaxis in HA patients with inhibitor (≥12 years of age) (HAVEN-1).[30] Dosing regimens were determined by the model-based simulation without dose escalation.[60] Patients who had received BPAs on demand were assigned to emicizumab prophylaxis (n = 35; group A) and no prophylaxis (n = 18; group B). Patients who had received prophylactic BPA treatment received emicizumab prophylaxis (group C). Emicizumab was administered at 3.0 mg/kg for 4 weeks, followed by 1.5 mg/kg weekly. Median ABRs were 2.9 (group A) and 23.3 (group B), indicating an 87% decrease in those receiving emicizumab prophylaxis. Moreover, 63% in group A had no bleeding events, compared with 6% in group B. Emicizumab prophylaxis in group C resulted in a significantly reduction of ABR (79%) compared with previous BPA prophylaxis. The most common treatment-related adverse events (AEs) were injection-site reactions (15%).[30] However, TMA (3 cases) and thrombotic events (2 cases) occurred at a concomitant therapy of emicizumab and aPCC administration. Five fatalities have been reported in patients who received emicizumab administration as compassionate use or expanded access during and after the clinical trial. However, the investigators or treating physicians determined that the cause of death was unrelated to emicizumab in each case (see emicizumab description in "Thromboembolic risk").[30]

Another phase 3 study (HAVEN-2) was established enrolling 57 HA children with inhibitors (2-12 years old).[61] In an interim analysis, 94.7% of patients did not require additional hemostatic treatment, and 64.9% of patients reported no bleeding events. The ABRs were 0.2 in emicizumab-treated children. A substantial reduction (99%) in ABR was observed with emicizumab prophylaxis compared with previous BPA treatment. Considerable improvements in health-related quality of life and other aspects of caregiver burden were seen. No thromboembolic events were observed. Mean steady-state emicizumab concentrations of ~50 μg/mL were maintained. Taken together, emicizumab prophylaxis led to a significantly lower rate of bleeding events in HA patients with inhibitor. However, 1 patient recently developed ADA (neutralizing antibody), and emicizumab treatment was consequently discontinued. Moreover, a recent report on a study involving nonhemophilic volunteers with a single injection reported that emicizumab-induced ADAs were detected in 3 out of 48 subjects (2/36 subcutaneously; 1/12 IV), suggesting a prevalence of ~5% for subcutaneous administration.[62]

Two additional phase 3 studies are currently ongoing: HAVEN-3[63]; emicizumab prophylaxis once weekly or every other week in HA patients without inhibitor (>12 years old) and HAVEN-4; and

emicizumab prophylaxis every 4 weeks in HA patients with or without inhibitor.

Fitusiran

A phase 1 dose-escalation study using subcutaneous administration was conducted in 4 healthy volunteers and 25 HA or HB patients without inhibitors.[64] Healthy volunteers received a single subcutaneous injection of fitusiran (0.03 mg/kg). Patients received 3 injections of fitusiran administered either once weekly (0.015, 0.045, or 0.075 mg/kg) or once monthly (0.225, 0.45, 0.9, or 1.8 mg/kg or a fixed dose of 80 mg). Single and weekly administration resulted in constantly low levels of plasma antithrombin. Monthly administration led to a predictable lowering of antithrombin levels by 70% to 90%, and a relationship between reduced levels of antithrombin and increased thrombin generation was observed in patients regardless of the type of hemophilia. The most common treatment-related AEs were injection-site reactions (~20%).[64]

On the basis of these results, a phase 2 study was conducted using subcutaneous administration of fitusiran at a 50 and 80 mg once-monthly dose in 14 inhibitor patients and 19 noninhibitor patients.[65] The interim data at a median of 13 months after the first administration demonstrated that patients at both dose levels had an ~80% decrease in antithrombin levels. The overall median ABR in fitusiran-treated patients without inhibitor was 1 compared with 12 (on demand) and 2 (prophylaxis) before the study, with 48% (16/33) of subjects experiencing no bleeding during the observation period. In addition, the median ABR in treated patients with inhibitor was 0 compared with 38 before the study, with 67% (22/33) of subjects reporting no spontaneous bleeds. All breakthrough bleeds were successfully controlled with replacement of FVIII(FIX) products or BPAs. Mean dose administrations per bleeds of aPCC or rFVIIa were 27 U/kg and 59 μg/kg, respectively. No thrombotic episodes were observed. Phase 3 studies using prophylactic fitusiran at 80 mg once monthly are ongoing in 3 clinical trials to further evaluate the safety and efficacy in hemophilia (with or without inhibitors). However, a sinus vein thrombosis was observed in a noninhibitor HA patient with the combination of fitusiran and FVIII product (see fitusiran description in "Thromboembolic risk").[31,66,67] Following this SAE, the fitusiran trials were immediately suspended. After widespread consideration of clinical risk and safety assessment, including the education strategy and protocol-specified guidelines (reduced dosing of FVIII or BPAs) to treat breakthrough bleeds in these circumstances, these trials have been reopened.

Concizumab

A single dose-escalation phase 1 study of concizumab (0.5-9,000 μg/kg IV or 50-3,000 μg/kg subcutaneously) was conducted in 24 HA or HB patients and 28 healthy volunteers.[68] Plasma concizumab levels were detectable for 43 days, and plasma concentrations of TFPI showing functional activity were decreased for 14 days after administration. There were no SAEs and no ADA. In a predosing phase 1 study, concizumab administered to 4 healthy males (250 μg/kg every other day, 8 doses) increased thrombin generation. Concizumab levels correlated positively with thrombin generation levels and negatively with TFPI levels. A phase 1 study investigating the safety, PK, and pharmacodynamics of multiple doses of concizumab (0.25, 0.5, or 0.8 mg/kg every 4 days) administered subcutaneously to HA patients was performed.[69] No safety concerns were evident, and the data confirmed a PK and pharmacodynamics relationship between the concizumab dose and TFPI levels and thrombin generation. Ten out of 15 (66.7%), 14 out of 30 (46.7%), and 6 out of 18 bleeding episodes (33.3%) at the 0.25, 0.5, and 0.8 mg/kg dose, respectively, required additional treatment. Concizumab levels of at least 100 ng/mL were most effective in reducing the frequency of bleeding episodes and thus more appropriate for prophylactic purposes. The dose-dependent increases in D-dimer and prothrombin fragments 1 and 2 were observed, but no ADA was reported. The most common treatment-related AE was injection-site reaction (n = 4). A phase 2 study has commenced to evaluate the efficacy of concizumab administered subcutaneously daily in HA and HB with or without inhibitors. A phase 1 study of 2 other anti-TFPI mAbs similar to concizumab, BAY-1093884 (Bayer) and PF-06741086 (Pfizer), has commenced.

Challenges to address for nonfactor products

Thromboembolic risk

Three TMAs and 2 VTEs (sinus vein thrombosis and superficial thrombophlebitis) under prophylactic emicizumab were recorded.[30,31] One patient developed TMA after 4 consecutive days of aPCC treatment for rectal bleeding, which was eventually fatal, although the TMA had resolved at the time of death. All thromboembolic events commonly occurred during adjunctive treatment with aPCC for breakthrough bleeds, and the thrombotic risk appeared to be dose related. All thrombotic events (5 out of 8 treatment episodes) occurred during aPCC treatment (>100 U/kg per day, >24 hours). Contrastingly, no events occurred with low doses of aPCC (≤100 U/kg per day), shorter treatment periods (<24 hours), or the use of rFVIIa for breakthrough bleeds.[30] Therefore, a recommendation was proposed for the treatment of breakthrough bleeds during emicizumab prophylaxis that included rFVIIa use and the lowest doses of approved BPAs but avoided the use of aPCC, if possible. No new thrombotic events were recorded after the implementation of these guidelines.

A thromboembolic event was reported in a noninhibitor HA patient with a concomitant therapy of fitusiran and FVIII product.[31,66,67] Supplementary therapeutic doses of FVIII (31-46 U/kg) were given for breakthrough bleeds, but the patient complained of a severe headache. A subarachnoid hemorrhage was diagnosed by computed tomography, and FVIII replacement was continued. The patient subsequently died of cerebral edema, and post hoc review of the initial computed tomography indicated that the initial event was a sinus vein thrombosis. After a risk-mitigation strategy that included an education strategy and protocol-specified guidelines (reduced dosing of FVIII or BPAs) to treat breakthrough bleeds, no new thrombotic events were recorded.

The increased incidence of thrombotic events is related to the fact that emicizumab activity depends on its ability to bridge the antigens FIXa and FX.[35] The development of TMA, however, centers on activated platelets under high-shear flow in arterial vessels and was a novel thromboembolic complication that was not previously reported during BPA administration. A possible explanation may be the shear stress–dependent formation of

ternary complexes at the surface of activated platelets. Some mechanisms may be further considered, including (1) enhanced formation of antibody/FcR complexes at the endothelial surfaces; (2) enhanced endothelial activation due to formation of ternary complexes at the endothelial surface due to FIX/FIXa accumulated at the endothelial cell surface, which may increase upon aPCC use (consequently higher local concentrations may promote FcR binding and/or FX activation); and (3) activation of complement proteases by ternary complexes. Precise mechanisms remain to be determined, however.

From these experiences, further basic research is required to fully characterize the functional mechanisms of these products and their reactions with concomitant BPA treatment. Further clinical investigations appear to be urgently needed to determine the appropriate doses of FVIII(FIX) products and BPAs used for breakthrough bleeds or surgical procedures under nonfactor products prophylaxis. In particular, the combined use of aPCC and emicizumab deserves significantly careful consideration. Easy-to-use techniques to monitor hemostasis during nonfactor product prophylaxis in these circumstances could be especially valuable.

Breakthrough bleeds

We may have fewer opportunities for hemostatic management of inhibitor patients treated with nonfactor products because of the greatly preventable effects of bleeding. Therefore, hemostatic treatment for breakthrough bleeds and surgery is a serious issue. HA patients treated with emicizumab were controllable by approved therapeutic dosage of BPAs at breakthrough bleeds.[30,58,59] However, thrombotic events occurred during aPCC treatment with >100 U/kg per day for >24 hours.[30] For the treatment of breakthrough bleeds, no thrombotic events have occurred since the recommendation of using rFVIIa initially (avoiding aPCC, if possible) and the lowest doses of approved BPAs. Breakthrough bleeds in inhibitor patients treated with fitusiran were initially controlled using a therapeutic dosage of BPAs (mean total amounts per bleed: aPCC, 40 U/kg; rFVIIa, 156 μg/kg).[64,65] A thrombotic event occurred with FVIII replacement in a noninhibitor patient.[31] The protocol-specified reduced dosing of FVIII or BPAs has been used for the treatment of breakthrough bleeds, and no thrombotic events have occurred. BPA treatment at breakthrough bleeds has not been reported in concizumab-treated inhibitor patients.[68,69] Taken together, hemostatic management using the recommended treatment regimen is currently warranted for breakthrough bleeds under nonfactor clotting prophylaxis.

Perioperative hemostatic management

Limited information is available on the perioperative hemostatic management of patients receiving nonfactor product prophylaxis. In this context, 29 emergent surgical procedures in 22 inhibitor patients treated with emicizumab were recorded (24 in HAVEN-1 and 5 in HAVEN-2).[70] A total of 20 and 9 operations were managed without and with BPA supplements, respectively. Six procedures were tooth extractions, and 9 procedures were related to central venous access devices. Twelve patients required minor surgery, and 2 patients needed major surgery (knee synovectomy, laparoscopic appendectomy). Nine procedures were covered with prophylactic BPAs (8 cases using rFVIIa [152 μg/kg, median of 1 injection] and one case using aPCC [49.7 U/kg, 1 injection]). Postoperative bleeding was observed in 6 out of 20 surgical procedures without prophylactic BPAs and in 1 BPA-treated case. Therefore, the majority of surgical procedures in emicizumab-treated patients were successfully managed without prophylactic BPAs, although postoperative bleeding requiring BPA intervention was necessary in ~30% of cases.

Five surgical procedures in 4 HA patients (2 inhibitor and 2 noninhibitor) treated with fitusiran have been reported.[71] Two inhibitor patients were treated with 80 mg once monthly. One patient had teeth extracted and was given rFVIIa (90 μg/kg, 3 times) for postoperative bleeding. The other required thoracotomy procedures and, at the investigator's discretion, was treated with standard dosing of FVIII (42-84 U/kg per day for 7 days), followed by BPAs (aPCC, 74-216 U/kg per day for 4 days; rFVIIa, 93 μg/kg per day for 3 days). Two noninhibitor patients (50 and 80 mg dose) had tooth extractions, endoscopic cholecystectomy, and nasal septoplasty and were managed with reduced doses of FVIII (14-28 U/kg per day). These studies demonstrated successful perioperative hemostatic management of patients receiving fitusiran prophylaxis.

Hemostatic monitoring

Another concern regarding nonfactor products prophylaxis is the establishment of effective laboratory assays to assess hemostatic control. Prophylaxis using these products seems to be highly effective in reducing bleeding episodes, however, and the need to regularly monitor this treatment may not be necessary under general circumstances. Nevertheless, consistent laboratory assessment could be essential to monitor hemostasis to avoid the prothrombotic status in patients treated with FVIII(FIX) or BPAs for breakthrough bleeds and in surgical situations or in ITI-considered cases. However, since none of the nonfactor products can be correlated with a known FVIII activity level, it is not possible to monitor these products in terms of FVIII equivalence.

Since emicizumab mimics FVIIIa cofactor function, the aPTT-shortening effect mediated by emicizumab is more pronounced than that of FVIII.[27] Consequently, FVIII activity and FVIII inhibiter titers, measured by an aPTT-based 1-stage clotting assay, are significantly influenced by emicizumab. We have recently reported the use of clot waveform analysis to assess the coagulation potential of emicizumab. This assay is based on the balance of the extent of activation of relevant coagulation proteins by optimizing aPTT and PT reagents, and the parameters could assess the coagulation potential of emicizumab without or with concomitant therapy of FVIII or BPAs.[72] We also have explored the usefulness of rotational thromboelastometry in whole blood in these circumstances.[73] However, since the assessments of these assays are based on ex vivo experiments, the hemostatic potential in vivo remains unclear. aPTT-based, 1-stage coagulation assays for the measurement of FVIII activity and FVIII inhibitor titers in the presence of emicizumab have been reported based on the neutralizing activity of 2 anti-idiotype antibodies against anti-FIX $F(ab')_2$ and anti-FX $F(ab')_2$.[74] Chromogenic assays with bovine-derived reagents are also being used. Advances with techniques of this nature for monitoring hemostasis during emicizumab prophylaxis could have a critical influence on the safety of their use.

Fitusiran and concizumab mediate significant, dose-dependent decreases of antithrombin and TFPI levels, both resulting in increased thrombin generation. A lowering of antithrombin by

>75% of the initial level by fitusiran led to increased thrombin generation in hemophilia patients, irrespective of the presence of inhibitors. Peak thrombin levels during treatment were at the lower end of the range observed in healthy volunteers.[64,65] Likewise, enhancement of thrombin generation, promoted by concizumab, correlated directly with antibody concentration and inversely with TFPI levels.[67,68] In ex vivo experiments, concizumab added to patients' plasma improved thrombin generation to near-normal ranges.[75] A comprehensive coagulation assay such this may be useful to measure the hemostatic potential of these products. This assay can be technically demanding, however, and its use in monitoring concomitant therapy with BPAs remains to be resolved. An aPTT-based assay appears to be possible to measure FVIII activity and Bethesda titer in the presence of fitusiran or concizumab according to the coagulation mechanisms of these products.

ITI

ITI is widely accepted as the primary approach to eradicate inhibitors.[76,77] Treatment is highly intensive, however, and requires frequent and long-term administration of FVIII(FIX) concentrates, often with the need for central venous access devices in children. Nonfactor product prophylaxis has the potential to reduce the need for ITI. Concerns about thromboembolic events in patients treated with BPAs or FVIII(FIX) for breakthrough bleeds and surgical procedures are pivotal, however, and the eradication of inhibitors at an early stage after inhibitor detection remains an important option. The advantages and disadvantages of ITI under nonfactor product prophylaxis are governed by several patient-specific circumstances, such as inhibitor titer, product availability, and laboratory facilities for hemostatic monitoring. Discussions on alternatives to ITI are likely to depend on individual circumstances. In addition, the observation would need to consider whether the long-term clinical efficacy (compared with FVIII/IX for nonfactor products) is good enough to replace clotting factors in noninhibitor patients, including those successfully treated with ITI.

Conclusions

The nature and development of nonfactor products currently available for hemophilia patients with inhibitor have been outlined, and the outcomes of recent clinical trials have been reviewed. The evidence suggests that this novel therapy could provide a new standard of care for hemophilia patients with inhibitor. Further studies are required, however, to accumulate conclusive clinical data on safety, especially regarding the risk of thromboembolism or TMA with the concomitant use of BPAs or FVIII(FIX). Standardized techniques to monitor hemostasis in those patients receiving nonfactor products will assist clinical management in these circumstances.

Authorship

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