Hemophilia and inhibitors: current treatment options and potential new therapeutic approaches

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The immune response to infused factor concentrates remains a major source of morbidity and mortality in the treatment of patients with hemophilia A and B. This review focuses on current treatment options and novel therapies currently in clinical trials. After a brief review of immune tolerance regimens, the focus of the discussion is on preventing bleeding in patients with hemophilia and inhibitors. Recombinant factor VIIa and activated prothrombin complex concentrates are the mainstays in treating bleeds in patients with inhibitors. Both agents have been shown to reduce bleeding episodes to a similar degree when infused prophylactically; however, individual patients may respond better to one agent over the other at any given time. The international immune tolerance trial revealed that a high-dose factor VIII regimen provided significantly better bleeding protection than the low-dose regimen. Given the high cost of treatment and the potential for a high-dose immune tolerance regimen to prevent bleeding in some patients, we discuss how we treat patients to maximize the prevention of bleeds while minimizing cost. Novel approaches to treatment of these patients are in development. These include agents that mimic factor VIII or augment thrombin generation by bypassing the inhibitor, as well as agents that inhibit the natural anticoagulants.

Learning Objectives

- Select an appropriate treatment regimen for preventing joint bleeding in patients with hemophilia and inhibitors
- Describe novel approaches to treating patients with hemophilia and inhibitors

Introduction

The prevention and treatment of bleeds with factor VIII (fVIII) and factor IX (fIX) replacement products have greatly improved the quality of care for patients with hemophilia A and B, respectively. However, development of neutralizing antibodies, or inhibitors, against infused factor remains a challenging complication of hemophilia treatment. Approximately ~30% of patients with severe hemophilia A will develop inhibitors, in addition to 5% of patients with mild and moderate hemophilia A and 3% of patients with hemophilia B.[1-3] Inhibitors significantly increase the cost of care, intensify the financial and psychosocial stressors on patients and their families, and have a negative effect on disease morbidity and mortality by making bleeding episodes more difficult to treat.[4,5] Despite the development of multiple innovative therapeutic products that treat bleeding and reduce disease burden in patients without inhibitors, bypassing agents (BPAs) are the primary treatment modalities currently available for patients with inhibitors. Therefore, novel approaches that address bleeding in the setting of antifactor inhibitors are an active area of investigation in the field. This review focuses on current therapeutic options to prevent joint bleeding and discusses the novel therapies in development for patients with hemophilia and inhibitors.

Immune tolerance induction

Immune tolerance induction (ITI) is considered the standard of care for inhibitor eradication in patients with hemophilia, predominantly in patients with severe hemophilia A. ITI refers to frequent and regular exposure to fVIII concentrates, often at high doses over the course of several months to years, as a method to induce tolerance. Proposed mechanisms of tolerance induction include T-cell exhaustion through overstimulation, and ultimately T-cell anergy, inhibition of fVIII-specific memory B-cell differentiation, and formation of anti-idiotypic antibodies.[6] After successful ITI, patients are able to resume the use of factor replacement therapies for prophylaxis and acute bleeding.

Patients with low titer and low responding inhibitors (<5 Bethesda units [BU]/mL) can often continue receiving factor replacement therapy, albeit at higher doses, for prophylaxis and treatment of bleeds. This group of inhibitors may include transient inhibitors that often resolve within 6 months. High-titer inhibitors are defined as those with inhibitor titers of 5 BU/mL or higher. In general, patients with inhibitor titers between 5 and 10 BU/mL are recommended to start ITI with high doses of fVIII as soon as possible.[7] Conversely, patients with inhibitor titers higher than 10 BU/mL, which is considered a poor-risk feature, have historically had ITI delayed until the inhibitor titer declined to less than 10 BU/mL, but recent publications have suggested a role in immediately starting ITI for these patients.[8]

The International Immune Tolerance study (IITI) is the only prospective randomized controlled trial evaluating the efficacy of ITI in patients with severe hemophilia A and good-risk features (Table 1). It compared low-dose (LD) 50 IU/kg thrice weekly vs high-dose (HD) 200 IU/kg daily fVIII regimens and demonstrated an ~70% overall

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Table 1. Risk stratification of inhibitor patients

	Good-risk features	Poor-risk features
Age at start of ITI	<8 y	≥8 y
Historical peak titer	<200 BU/mL	≥200 BU/mL
Pre-ITI titer	<10 BU/mL	≥10 BU/mL
Time to titer decline to <10 BU/mL before ITI	<24 mo	≥24 mo

Data from Kempton and Meeks.[7]

success rate.[9-11] The time to negative inhibitor titer and normal fVIII recovery was shorter in the high-dose group, although both dosing groups had similar rates of tolerance. For patients with hemophilia B and inhibitors, 31% achieved tolerance at dosing regimens ranging from 25 to 200 IU/kg/day.[9] Distinct from fVIII inhibitors, fIX inhibitors can manifest with allergic reactions, anaphylaxis, and nephrotic syndrome, which can complicate the decision to pursue ITI. In addition, there is insufficient evidence to recommend a specific regimen for desensitization, immune tolerance, and immunosuppression, as the data are primarily limited to case reports or series.[12-14]

In patients with severe hemophilia A and poor-risk features, outcome data on ITI are limited to observational studies. In the North American Immune Tolerance Registry, 40% patients with a pre-ITI titer of 10 BU/mL or higher achieved successful tolerance compared with 83% of those with pre-ITI titers lower than 10 BU/mL.[9] However, in a single-center study of late ITI (ie, ITI initiated 2 or more years from inhibitor detection) in patients with poor-risk features, 4 of 9 patients (44%) were successfully tolerized, and an additional 3 patients (33%) were partially tolerized, demonstrating an inhibitor titer lower than 5 BU/mL and the ability to treat bleeds with fVIII products.[15] Although lower rates of successful tolerance are anticipated in patients with poor-risk features, there is a subset of patients who respond to ITI, and continual assessment of their inhibitor status is warranted. There are multiple excellent reviews of ITI and recommendations for practice that were published after the IITI study that can be referenced for a more in-depth discussion.[16,17]

Treatment options for bleeding

BPAs provide hemostasis through pathways that circumvent the need for fVIII or fIX to generate thrombin. The 2 currently available BPAs are recombinant fVIIa (rfVIIa; Novoseven RT, Novo Nordisk) and activated prothrombin complex concentrate (aPCC; FEIBA VH, Baxalta). Both rVIIa and aPCC have shown ~80% hemostatic efficacy in patients with hemophilia with inhibitors in a variety of clinical settings with rare incidents of thromboembolism.[18-20] The FENOC study compared the efficacy of rVIIa and aPCC in patients with hemophilia A and inhibitors in a prospective, randomized crossover trial of clinical equivalency.[21] Analysis of 96 bleeding episodes in 48 patients demonstrated 80.9% efficacy with aPCC and 78.7% efficacy with rVIIa 6 hours after treatment of joint bleeds. Interestingly ~30% to 40% of patients who received both rfVIIa and aPCC reported improved hemostatic efficacy and stoppage of bleeds with one agent over the other up to 12 hours after infusion. A portion of patients alternated between favoring one agent over the other, whereas 10% of participants responded to neither product.

Prophylaxis in patients with inhibitors

Prophylaxis is the standard of care for patients with severe hemophilia but may not be feasible for patients with inhibitors because of cost, increased infusion frequency (rfVIIa), large infusion volumes (aPCC), theoretical risk for thrombosis, and incomplete correction of the hemostatic defect that results in more breakthrough bleeds. Despite these limitations, patients with inhibitors often benefit from prophylaxis therapy with BPAs pending the start of ITI, during ITI, and indefinitely if ITI fails for prevention of recurrent joint bleeds, hemophilic arthropathy, and subsequent disability.[22,23] Prospective studies of both aPCC (85 U/kg on 3 nonconsecutive days/week) and rfVIIa (90 μg/kg/day and 270 μg/kg/day) reduced bleeding when compared with on-demand regimens.[24,25] Furthermore, prophylaxis improved quality of life, reduced hospitalizations, and reduced the number of patient-reported missed days from work or school.[26]

Bleeding protection during ITI is also important. Twice-daily administration of an aPCC during ITI with high-dose fVIII was a component of the initial phase of the Bonn ITI protocol, and ~66% of patients in this cohort showed favorable orthopedic outcomes after therapy completion.[27] An important finding in the IITI study was the significant increase in bleeding in the LD fVIII group compared with in the HD group (hazard ratio, 2.20; $P = .0019$) in spite of comparable rates of tolerance. Discrepancies in bleeding rates, particularly in the early phase of tolerance between the start of ITI and a negative inhibitor titer, resulted in a trend toward increased hospitalizations (72 in the LD group vs 39 in the HD group; $P = .145$) and a lower number of participants without bleeding during the ITI course (14% in the LD group vs 37% in the HD group; $P = .0085$) in the LD group. The study was ultimately terminated prematurely as a result of these findings and study futility. Effect of prophylaxis during ITI on bleeding rates could not be assessed because of a limited number of participants treated with BPA prophylaxis.

How we treat

Traditionally, the use of BPAs during ITI has been reserved for patients with inhibitor titers higher than 10 BU/mL and persistent bleeding symptoms despite high doses of fVIII replacement. As BPA prophylaxis before the initiation of ITI has become more routine, many providers are continuing this with the start of ITI. Given the high cost of BPA prophylaxis and clear data from the IITI study that there was less bleeding in patients receiving high-dose ITI, deciding when and whether BPA prophylaxis is added to ITI in addition to when BPA prophylaxis can be stopped because the high-dose fVIII is enough can be a challenge. The following highlights these decision points and how we treat these patients.

Choosing a BPA

The decision to use one BPA over the other depends on multiple factors, including the phase of ITI therapy, bleeding frequency, patient convenience (ie, dosing frequency and infusion volumes), and clinical efficacy for the patient.[28,29] rVIIa is often chosen as the first-line BPA for patients with hemophilia A and B with inhibitors before the start of ITI because of the potential risk for anamnesis and allergic reaction with aPCC resulting from small amounts of fVIII and the presence of fIX, respectively. There is a theoretical higher thrombotic risk with high doses of either agent, although very few cases of thrombosis have been reported.[24,25] Table 2 reviews the advantages and disadvantages of the currently available agents. It is important to note that a portion of patients will not respond to either agent, and that the response to each of these agents can change over time in the same patient, warranting routine reassessment of hemostatic efficacy of the treatment regimen during clinic visits. Predicting what agent a patient will respond to, and treating patients who do not respond to either agent, remains a challenge. For patients

Table 2. Comparison of available BPAs for patients with hemophilia A and inhibitors

	rfVIIa	aPCC
Brand name	Novoseven RT	FEIBA VH
Product type	Recombinant	Plasma-derived, virally inactivated
Product contents	fVIIa	fII, fIX, fX, fVIIa
Half-life	2-3 h	8-12 h
Treatment dosing[17]	90-120 μg/kg every 2-3 h or 270 μg/kg × 1	50-100 IU/kg every 8-12 h (max dose, 200 IU/kg/day)
Prophylaxis dosing[24,25]	90 or 270 μg/kg daily	85 IU/kg 3 times per week
Infusion volume*	1 mg/mL (2 ml)	~40 IU/mL (40 mL)
Advantages	Lower infusion volumes No risk for anamnesis	Less frequent dosing regimens
Disadvantages	Frequent dosing regimens	Large infusion volumes Risk for anamnestic response Contraindicated in patients with hemophilia B with inhibitors
General disadvantages of both agents	Requirement of reliable venous access Expensive and cost prohibited in some centers Small theoretical risk for thrombosis No reliable biomarkers available to correlate with therapeutic dosing or efficacy Incomplete hemostatic effect compared with replacement factor in patients without inhibitors	

*Infusion volume based on a 20-kg child with doses of rVIIa 2 mg and aPCC 1600 IU.

who have failed ITI, the decision between BPAs is based on hemostatic response and patient preference.

On-demand vs prophylaxis with BPAs in inhibitor patients receiving ITI

Patients with hemophilia A that present with high responding inhibitors between 5 and 10 BU/mL are started on high-dose fVIII at 100 to 200 IU/kg/d as soon as possible. Often these patients need central access to accomplish this. We initially attempt continuous infusion of fVIII (6-10 U/kg/h to achieve fVIII levels of 80%-100%), and the majority of these patients are successfully covered through port placement and then transitioned to ITI dosing. If adequate fVIII levels cannot be obtained, patients are covered with BPAs for their port placement while starting on daily ITI. The BPAs are stopped after 7 to 10 days and restarted only if bleeding occurs. For patients with titers higher than 10 BU/mL who will start ITI immediately, central access, if needed, is placed with rfVIIa coverage. Once healed, high-dose ITI at 100 to 200 IU/kg/d is initiated, and a BPA is added if breakthrough bleeding occurs, such as recurrent joint bleeds, large hematomas, and so on. High-titer inhibitor patients who start receiving BPA prophylaxis for a period of time before ITI initiation typically continue on the same agent once ITI has started. Depending on the bleeding pattern, it is reasonable to start high-dose ITI and then add BPA prophylaxis if bleeding occurs, acknowledging the higher risk for life-threatening bleeding. Given the cost of BPA prophylaxis, we initially treat most patients with high-dose fVIII alone unless they have a history of intracranial hemorrhage or other major bleeding. A single joint bleed is sufficient to start BPA prophylaxis in these patients to prevent long-term sequelae. Assessing the need for on-demand therapy or prophylaxis with BPAs involves regular monitoring of the bleeding frequency, hemostatic response to high-dose fVIII, and trend of the inhibitor titer. It is recommended that patients are followed monthly during ITI until a negative inhibitor titer is achieved, at which time they can be transitioned to every-3-month monitoring[16]; however, this is primarily based on consensus recommendations because of the lack of data evaluating the optimal frequency of monitoring.

When to discontinue BPA prophylaxis

Anti-fVIII inhibitor titer, as measured by the Bethesda assay and fVIII levels, are monitored regularly in the clinic to trend the inhibitor titer and assess for fVIII recovery. We have routinely seen some level of factor recovery as the titer drops below 100 BU/mL and begin checking peak fVIII levels (fVIII activity 15 minutes after an infusion) during routine inhibitor monitoring visits. The majority of patients have measurable recovery before their titers drop below 10 to 20 BU/mL, and we frequently observe not only measurable fVIII levels but also high fVIII levels (>100%) before achieving a negative inhibitor titer. Any measurable peak recovery higher than 10% is evaluated further. The kinetics of fVIII inhibition are assessed both in the laboratory and in the clinic with further pharmacokinetics to evaluate whether a patient would be a good candidate to stop BPAs, as illustrated in the case presented here, or if levels are high enough immediately after infusion that the timing of the dose of BPA should be spaced apart from fVIII to limit the risk for thrombosis.

Case: An 18-month-old with severe hemophilia A, who initially presented with an inhibitor titer of 40 BU/mL after circumcision, was started on ITI at 200 U/kg/d, and rfVIIa was added shortly afterward secondary to bleeding at his port site with access. His titer peaked at ~1000 BU/mL in the first month, and 6 months later was down to 75 BU/mL. His father reported that he no longer seemed to have bleeding after port access. After his dose of 200 IU/kg fVIII, a peak fVIII level in clinic returned at 4%, and subsequent testing showed a persistent fVIII level of 4% 6 hours later. Subsequently, his BPA prophylaxis was stopped. He has had no joint bleeds off BPA prophylaxis now for more than 1 year, with titers ranging from 34 to 166 BU/mL. He has had multiple traumatic injuries/lacerations to his face, which have required on-demand use of BPAs, but no joint bleeds.

Given the individual characteristics of each inhibitor patient, the timing of initiation and discontinuation of BPAs must be constantly evaluated. Hemostatic efficacy, fVIII recovery, and inhibitor titer should be monitored closely, especially after the titer falls below

Table 3. Summary of novel therapies for patients with hemophilia and inhibitors currently in clinical trial

Category	Agent	Mechanism of action	Administration	Drug half-life	Clinical trial status
"Targeting the on switch"	Emicizumab (ACE910)	Bispecific antibody binds fIXa and fX mimicking fVIIIa to generate thrombin	Subcutaneous injection (weekly vs monthly dosing)	~30 d (healthy subjects)	Preclinical completed[50] Phase 1 completed[30] Phase 2/3 ongoing
"Targeting the off switch"	Fitusiran (ALN-AT3)	Antithrombin knockdown via siRNA interference of hepatic AT3 mRNA translation and gene expression	Subcutaneous injection	7 d	Phase 1 ongoing[36,37,51] Phase 2/3 due to enroll in 2017
	Concizumab (MAb 2021)	TFPI inhibitor	Subcutaneous injection or intravenous infusion	7 d	Preclinical completed[38] Phase 1 completed[39]
Other agents	rfVIIa-FP (CSL689)	Extended half-life rfVIIa and albumin fusion protein	Intravenous infusion	~6-10 h	Preclinical completed[42] Phase 1 completed[43] Phase 2/3 enrolling
	Obizur (OBI-1, BAX801)	B-domain deleted porcine factor replacement product	Intravenous infusion (on-demand dosing)	~10-12 h[48] (patients with hemophilia A)	US Food and Drug Administration approved 2014 for acquired hemophilia A (U.S.)
		Reduced cross-reactivity with anti-human fVIII inhibitors		Estimations will vary, depending on the presence of underlying cross-reactive antibodies	Phase 1-3 completed for acquired hemophilia A indication
					Phase 1/2 in patients with congenital hemophilia A and inhibitors completed[48,49]

100 BU/mL, to ensure the best possible balance between bleeding protection and cost of prophylaxis.

Novel agents

Given the limitations of BPAs and lack of alternative agents for bleeding prevention and treatment in inhibitor patients, there are several promising new therapies currently in clinical trials addressing these deficiencies (Table 3). We have classified these novel agents into 2 predominant categories: therapies that target aspects of the coagulation cascade that promote thrombin generation with subsequent clot formation (ie, "turn on the on switch") and therapies that target the anticoagulant regulators of the cascade (ie, "turn off the off switch"). Additional agents that use alternate mechanisms for bleeding prevention/treatment will be reviewed briefly.

"Turning on the on switch"

Bispecific fIXa/X antibody. Amplification of the coagulation cascade to generate the thrombin burst that ultimately leads to stable clot formation is mediated by the intrinsic Xase complex. This complex consists of activated fVIII (fVIIIa) serving as a cofactor for activated fIX (fIXa) on a phospholipid surface to generate activated factor Xa (fXa) from factor X (fX). Emicizumab (ACE910) is a recombinant humanized bispecific antibody that mimics fVIIIa cofactor activity through high-affinity binding of fIXa and fX supporting thrombin generation. In the single-center phase 1 double-blinded, randomized control trial, pharmacokinetic studies showed an average half-life of 28.3 to 34.4 days in 64 healthy Japanese and American subjects after 1 subcutaneous injection of ACE910.[30] Two of 48 subjects were found to have antidrug antibodies, 1 of which had antidrug antibodies before drug exposure that did not alter plasma drug concentration, activated partial thromboplastin time, or peak thrombin compared with other subjects. In a separate trial of 18 Japanese patients with severe hemophilia A, once-weekly subcutaneous injections of ACE910 over the course of 12 consecutive weeks at 0.3, 1, or 3 mg/kg reduced annualized bleeding rate by 90% to 100% (median follow-up time, 9.5 months) compared with on-demand therapy with BPAs before trial enrollment.[31] Study participants were able to infuse fVIII products or BPAs as needed for on-demand treatment of bleeds during the trial period. There were no thromboembolic events observed. Phase 2/3 trials in adult and pediatric patients with severe hemophilia A with and without inhibitors are currently underway or scheduled to open.

"Turning off the off switch"

Antithrombin knockdown. Antithrombin is an important negative regulator of excess thrombin formation via thrombin and fXa inhibition. Individuals with inherited or acquired deficiencies of antithrombin have an increased risk for thrombosis.[32,33] Balancing the bleeding phenotype in hemophilia with the mild prothrombotic phenotype seen in antithrombin deficiency is the rationale behind the development of a small interfering RNA (siRNA) ALN-AT3. The siRNA technology allows for targeted interference of post-transcription gene expression at sites of endogenous protein production of specific genes by interfering with mRNA translation.[34] The siRNA ALN-AT3, Fitusiran, is conjugated to *N*-acetylgalactosamine, a ligand for the asialoglycoprotein receptor that facilitates delivery of siRNAs to hepatocytes through high-affinity interaction.[35] ALN-AT3 specifically targets and disrupts antithrombin mRNA production in the liver, resulting in increased thrombin generation. In the multicenter phase 1 trial, no thromboembolic events or significant alterations in thrombotic parameters occurred in healthy adult volunteers or patients with moderate or severe hemophilia A and B after a single subcutaneous dose of ALN-AT3.[36] Antithrombin lowering and elevated thrombin generation correlated with reduced annualized bleeding rate in patients with hemophilia receiving weekly drug administration compared with historical

controls on on-demand factor therapy. Furthermore, 12 hemophilia A and B inhibitor plasmas with 50% and 90% antithrombin knockdown using an antithrombin antibody showed increased peak thrombin generation without overcorrection beyond values observed in normal controls.[37] Questions remain on the thromboembolic risk and appropriate dosing regimen for factor replacement in the setting of bleeding and surgery.

Inhibition of natural anticoagulants. Activation of fX on a phospholipid membrane by tissue factor (TF)/fVIIa is negatively regulated by TF pathway inhibitor (TFPI). Concizumab, MAb 2021, is a humanized anti-TFPI monoclonal antibody that binds the TFPI Kunitz-2 domain with high affinity (the fXa binding site on TFPI) and alters TFPI inhibition of fXa. Preclinical studies in a rabbit hemophilia A model demonstrated reduced cuticle bleeding after Concizumab administration.[38] Decreased free and functional TFPI were measured in healthy adult volunteers and patients with severe hemophilia A or B without inhibitors after a single intravenous or subcutaneous dose of Concizumab in the phase 1 randomized, placebo-controlled trial.[39] Although bleeding rates were not a measured outcome in this study, the authors reported an absence of bleeding events at high plasma levels of Concizumab, with the exception of a minor trauma-induced finger cut. All patients remained on their standard on-demand or prophylaxis regimens with factor products during the trial. There were no antidrug antibodies formed or serious adverse events observed.

Aptamer technology has been applied to TFPI as another method to inhibit TFPI. Aptamers are single-stranded oligonucleotides that bind a specific target protein with high affinity. BAX499 is a polyethylene glycol-conjugated aptamer that binds to TFPI (Kunitz-1 and Kunitz-3 domains) and blocks TFPI inhibition of fXa and fVIIa. The aptamer improved whole-blood clotting times, clot formation, and thrombin generation in plasmas of patients with hemophilia A and B.[40] The phase 1 clinical trial was terminated early as a result of increased bleeding phenotypes in patients with hemophilia and elevated full-length TFPI levels. This was ultimately attributed to partial TFPI inhibition and inhibited TFPI clearance as a result of aptamer binding of the Kunitz-3 C-terminal domain of TFPI.[41]

Other agents

A recombinant fVIIa fusion protein that links rfVIIa to albumin (rfVIIa-FP) is a promising agent that has shown extended half-lives in a variety of species (ie, mice, rats, rabbits, monkeys) compared with rfVIIa.[42] The phase 1 randomized, placebo-controlled trial demonstrated half-life extension 3- to 4-fold greater (range, 6.1-9.7 h) than rVIIa after a single intravenous infusion of rfVIIa-FP in healthy volunteers.[43] There were no antidrug antibodies or serious adverse events. Phase 2/3 trials in patients with hemophilia A and B with inhibitors are currently enrolling. There have been other bioengineered extended half-life rfVIIa products, including glycopegylated rfVIIa (N7-GP) and BAY86-6150, developed; however, the clinical trials were prematurely stopped because of a lack of a dose-response or development of neutralizing antidrug antibodies with rfVIIa cross-reactivity in a patient with hemophilia with inhibitors.[44,45]

Recently, a recombinant B-domain deleted porcine fVIII (rpfVIII) product, Obizur (Baxalta), was approved by the US Food and Drug Administration for use in patients with acquired hemophilia A.[46] rpfVIII functions as a replacement fVIII therapy because of reduced cross-reactivity with antihuman fVIII inhibitors as a result of nonhomologous differences in sequence identity between porcine and human fVIII.[47] A randomized, placebo-controlled phase 1 trial of 9 patients with congenital hemophilia A and a history of inhibitors evaluated the safety and pharmacokinetics of a single dose of rpfVIII (n = 4) vs a highly purified plasma-derived pfVIII Hyate:C (Ipsen; n = 5).[48] Similar fVIII activity was achieved after rpfVIII and Hyate:C infusions without significant anti-porcine fVIII inhibitors. In a phase 2 open-labeled trial, rpfVIII demonstrated hemostatic efficacy and safety in 9 patients with congenital hemophilia A and inhibitors.[49] Larger, phase 2/3 studies are necessary to determine whether porcine fVIII would provide durable hemostatic efficacy in patients with congenital hemophilia A with inhibitors.

Conclusions

Inhibitors remain a challenging complication of treatment in patients with hemophilia. The process of inhibitor eradication through immune tolerance therapy is the standard of care and optimal long-term strategy for prevention of future bleeds and restoration of factor efficacy. However, ITI is a time-intensive and costly commitment that can impose substantial psychological and financial stressors on families. There are currently limited available agents beyond the BPAs to prevent and treat bleeding in inhibitor patients who have frequent bleeding episodes, fail ITI, relapse, or present with poor-risk features at high risk for ITI failure. Several questions remain regarding the optimal therapeutic approach in poor-risk patients. Nonetheless, there are several novel therapies in development or active clinical trials that may potentially lessen the burden of disease and reduce bleeding risk in patients with hemophilia with or without inhibitors.

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References

1. Dimichele D. Inhibitors: resolving diagnostic and therapeutic dilemmas. *Haemophilia*. 2002;8(3):280-287.
2. DiMichele D. Inhibitor development in haemophilia B: an orphan disease in need of attention. *Br J Haematol*. 2007;138(3):305-315.
3. Eckhardt CL, van Velzen AS, Peters M, et al; INSIGHT Study Group. Factor VIII gene (F8) mutation and risk of inhibitor development in nonsevere hemophilia A. *Blood*. 2013;122(11):1954-1962.
4. Lindvall K, von Mackensen S, Elmståhl S, et al. Increased burden on caregivers of having a child with haemophilia complicated by inhibitors. *Pediatr Blood Cancer*. 2014;61(4):706-711.
5. Guh S, Grosse SD, McAlister S, Kessler CM, Soucie JM. Healthcare expenditures for males with haemophilia and employer-sponsored insurance in the United States, 2008. *Haemophilia*. 2012;18(2): 268-275.
6. Waters B, Lillicrap D. The molecular mechanisms of immunomodulation and tolerance induction to factor VIII. *J Thromb Haemost*. 2009;7(9): 1446-1456.
7. Kempton CL, Meeks SL. Toward optimal therapy for inhibitors in hemophilia. *Blood*. 2014;124(23):3365-3372.
8. DiMichele DM, Hoots WK, Pipe SW, Rivard GE, Santagostino E. International workshop on immune tolerance induction: consensus recommendations. *Haemophilia*. 2007;13(suppl 1):1-22.
9. DiMichele DM, Kroner BL; North American Immune Tolerance Study Group. The North American Immune Tolerance Registry: practices, outcomes, outcome predictors. *Thromb Haemost*. 2002; 87(1):52-57.

10. Hay CR, DiMichele DM; International Immune Tolerance Study. The principal results of the International Immune Tolerance Study: a randomized dose comparison. *Blood*. 2012;119(6):1335-1344.
11. Mariani G, Kroner B; Immune Tolerance Study Group (ITSG). Immune tolerance in hemophilia with factor VIII inhibitors: predictors of success. *Haematologica*. 2001;86(11):1186-1193.
12. Batorova A, Morongova A, Tagariello G, Jankovicova D, Prigancova T, Horakova J. Challenges in the management of hemophilia B with inhibitor. *Semin Thromb Hemost*. 2013;39(7):767-771.
13. Shibata M, Shima M, Misu H, Okimoto Y, Giddings JC, Yoshioka A. Management of haemophilia B inhibitor patients with anaphylactic reactions to FIX concentrates. *Haemophilia*. 2003;9(3):269-271.
14. Bon A, Morfini M, Dini A, et al. Desensitization and immune tolerance induction in children with severe factor IX deficiency; inhibitors and adverse reactions to replacement therapy: a case-report and literature review. *Ital J Pediatr*. 2015;41:12.
15. Meeks SL, Chapman RL, Kempton C, Dunn AL. Late immune tolerance induction in haemophilia A patients. *Haemophilia*. 2013;19(3):445-448.
16. Valentino LA, Kempton CL, Kruse-Jarres R, Mathew P, Meeks SL, Reiss UM; International Immune Tolerance Induction Study Investigators. US Guidelines for immune tolerance induction in patients with haemophilia A and inhibitors. *Haemophilia*. 2015;21(5):559-567.
17. Collins PW, Chalmers E, Hart DP, Liesner R, Rangarajan S, Talks K, Williams M, Hay CR; UK Haemophilia Centre Doctors. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). UK Haemophilia Centre Doctors Organization. *Br J Haematol*. 2013;160(2):153-170.
18. Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. *J Thromb Haemost*. 2004;2(6):899-909.
19. Ehrlich HJ, Henzl MJ, Gomperts ED. Safety of factor VIII inhibitor bypass activity (FEIBA): 10-year compilation of thrombotic adverse events. *Haemophilia*. 2002;8(2):83-90.
20. Abshire T, Kenet G. Safety update on the use of recombinant factor VIIa and the treatment of congenital and acquired deficiency of factor VIII or IX with inhibitors. *Haemophilia*. 2008;14(5):898-902.
21. Astermark J, Donfield SM, DiMichele DM, et al; FENOC Study Group. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. *Blood*. 2007;109(2):546-551.
22. Ettingshausen CE, Kreuz W. Early long-term FEIBA prophylaxis in haemophilia A patients with inhibitor after failing immune tolerance induction: A prospective clinical case series. *Haemophilia*. 2010;16(1):90-100.
23. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357(6):535-544.
24. Leissinger C, Gringeri A, Antmen B, et al. Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors. *N Engl J Med*. 2011; 365(18):1684-1692.
25. Konkle BA, Ebbesen LS, Erhardtsen E, et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. *J Thromb Haemost*. 2007;5(9):1904-1913.
26. Hoots WK, Ebbesen LS, Konkle BA, et al; Novoseven (F7HAEM-1505) Investigators. Secondary prophylaxis with recombinant activated factor VII improves health-related quality of life of haemophilia patients with inhibitors. *Haemophilia*. 2008;14(3):466-475.
27. Brackmann HH, Oldenburg J, Schwaab R. Immune tolerance for the treatment of factor VIII inhibitors–twenty years' 'bonn protocol'. *Vox Sang*. 1996;70(suppl 1):30-35.
28. Monahan PE, Aledort LM; Hemophilia Inhibitor Study Group. Factors affecting choice of hemostatic agent for the hemophilia patient with an inhibitor antibody. *Am J Hematol*. 2004;77(4):346-350.
29. Valentino LA, Carcao M, Mathew P, et al. The application of bypassing-agent prophylaxis in haemophilia A patients with inhibitors: a meeting report. *Haemophilia*. 2009;15(4):959-965.
30. Uchida N, Sambe T, Yoneyama K, et al. A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects. *Blood*. 2016;127(13):1633-1641.
31. Shima M. The potential of bispecific antibodies for treatment of hemophilia A [abstract]. *J Thromb Haemost*. 2015;13(suppl 2). Abstract AS015.
32. Zöller B, García de Frutos P, Hillarp A, Dahlbäck B. Thrombophilia as a multigenic disease. *Haematologica*. 1999;84(1):59-70.
33. Ornaghi S, Barnhart KT, Frieling J, Streisand J, Paidas MJ. Clinical syndromes associated with acquired antithrombin deficiency via microvascular leakage and the related risk of thrombosis. *Thromb Res*. 2014;133(6):972-984.
34. de Fougerolles A, Vornlocher HP, Maraganore J, Lieberman J. Interfering with disease: a progress report on siRNA-based therapeutics. *Nat Rev Drug Discov*. 2007;6(6):443-453.
35. Nair JK, Willoughby JL, Chan A, et al. Multivalent N-acetylgalactosamine-conjugated siRNA localizes in hepatocytes and elicits robust RNAi-mediated gene silencing. *J Am Chem Soc*. 2014;136(49):16958-16961.
36. Pasi KJ, Georgiev P, Mant T, et al. A subcutaneously administered investigational RNAi therapeutic (ALN-AT3) targeting antithrombin for treatment of hemophilia: interim weekly and monthly dosing results in patients with hemophilia A or B. *Blood*. 2015;126(23):551.
37. Kenet G, Livnat T, Fosbury E, et al. Antithrombin reduction corrected thrombin generation in samples from hemophilia A and B patients with inhibitors. *Blood*. 2015;126(23):552.
38. Hilden I, Lauritzen B, Sørensen BB, et al. Hemostatic effect of a monoclonal antibody mAb 2021 blocking the interaction between FXa and TFPI in a rabbit hemophilia model. *Blood*. 2012;119(24):5871-5878.
39. Chowdary P, Lethagen S, Friedrich U, et al. Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial. *J Thromb Haemost*. 2015;13(5):743-754.
40. Gorczyca ME, Nair SC, Jilma B, et al. Inhibition of tissue factor pathway inhibitor by the aptamer BAX499 improves clotting of hemophilic blood and plasma. *J Thromb Haemost*. 2012;10(8):1581-1590.
41. Dockal M, Hartmann R, Knappe S, et al. Effect of increased tissue factor pathway inhibitor (TFPI) levels on factor Xa inhibition and global hemostasis in the presence of TFPI-antagonistic aptamer BAX 499. *Blood*. 2012;120(21):2207.
42. Zollner S, Schuermann D, Raquet E, et al. Pharmacological characteristics of a novel, recombinant fusion protein linking coagulation factor VIIa with albumin (rVIIa-FP). *J Thromb Haemost*. 2014;12(2):220-228.
43. Golor G, Bensen-Kennedy D, Haffner S, et al. Safety and pharmacokinetics of a recombinant fusion protein linking coagulation factor VIIa with albumin in healthy volunteers. *J Thromb Haemost*. 2013;11(11):1977-1985.
44. Ljung R, Karim FA, Saxena K, et al; Pioneer™1 Investigators. 40K glycoPEGylated, recombinant FVIIa: 3-month, double-blind, randomized trial of safety, pharmacokinetics and preliminary efficacy in hemophilia patients with inhibitors. *J Thromb Haemost*. 2013;11(7):1260-1268.
45. Koh PL, Ng HJ, Lissitchkov T, Hardtke M, Schroeder J. The TRUST trial: anti-drug antibody formation in a patient with hemophilia with inhibitors after receiving the activated factor VII product Bay 86-6150. *Blood*. 2013;122(21):573.
46. Janbain M, Leissinger CA, Kruse-Jarres R. Acquired hemophilia A: emerging treatment options. *J Blood Med*. 2015;6:143-150.
47. Lillicrap D, Schiviz A, Apostol C, et al. Porcine recombinant factor VIII (Obizur; OBI-1; BAX801): product characteristics and preclinical profile. [published online ahead of print 17 August 2015]. *Haemophilia*. doi: 10.1111/hae.12784. 2015.
48. Kempton CL, Abshire TC, Deveras RA, et al. Pharmacokinetics and safety of OBI-1, a recombinant B domain-deleted porcine factor VIII, in subjects with haemophilia A. *Haemophilia*. 2012;18(5):798-804.
49. Mahlangu J, Andreeva TA, Macfarlane D, et al. A phase II open-label study evaluating hemostatic activity, pharmacokinetics and safety of recombinant porcine factor VIII (OBI-1) in hemophilia A patients with alloantibody inhibitors directed against human FVIII. *Blood*. 2007;110(11):783.
50. Muto A, Yoshihashi K, Takeda M, et al. Anti-factor IXa/X bispecific antibody (ACE910): hemostatic potency against ongoing bleeds in a hemophilia A model and the possibility of routine supplementation. *J Thromb Haemost*. 2014;12(2):206-213.
51. Sehgal A, Barros S, Ivanciu L, et al. An RNAi therapeutic targeting antithrombin to rebalance the coagulation system and promote hemostasis in hemophilia. *Nat Med*. 2015;21(5):492-497.