REVIEW ARTICLE

Thrombosis Complicating Non-Factor Therapy for Hemophilia

Author

Margaret V Ragni

University of Pittsburgh

Email: ragni@pitt.edu

Abstract

This is an exciting time in hemophilia treatment with the unprecedented development of novel non-factor therapies. These agents have re-balanced hemostasis in patients with hemophilia A and B, with and without inhibitors, tipping the balance toward hemostasis and improved thrombin generation. While there have been numerous publications about the beneficial hemostatic effects and significant bleed reduction possible with these novel non-factor agents, little has been written about the less well-recognized thrombotic complications. Yet, the latter underscores the fine balance between hemostasis and thrombosis and the fact these agents *prevent* but do not *treat* bleeds, requiring clotting factor requirement to treat acute bleeds. The purpose of this Commentary is to review thrombotic complications that have occurred with non-factor therapies, risk factors for thrombosis, potential mechanisms, and potential mitigation approaches.

Key Words: hemophilia, non-factor therapy, rebalanced hemostasis, thrombosis

Introduction

Hemophilia is an X-linked disorder affecting males and associated with spontaneous and traumatic bleeds into joints, muscles, and body cavities. The defective or deficient factor VIII (hemophilia A) or factor IX (hemophilia B) results in reduced thrombin generation and fibrin clot formation and impairs hemostasis. Thus, treatment of hemophilia requires clotting factor several times weekly to prevent bleeds (prophylaxis), but it is costly, invasive, and burdensome. Yet this is an amazing time in hemophilia, with unprecedented innovation that has led to the development of novel non-factor therapies. These agents rebalance hemostasis by modifying pro- and anticoagulant pathways to improve thrombin generation. They simplify treatment by subcutaneous administration and reduce bleeds in those with and without inhibitors, e.g. anti-factor VIII or anti-factor IX, greatly improving clinical outcomes and quality of life. Yet, there have been unforeseen complications, the most serious of which is thrombosis, both arterial and venous. Whether thrombosis relates to the degree to which these agents, by differing mechanisms, disrupt the delicate hemostatic balance, or the requirement for factor to treat acute bleeds, tipping it towards thrombosis, is not known. The purpose of this review is to consider mechanism by which each novel agent rebalances hemostasis, the mechanisms by which these thrombotic events may occur, and potential strategies to mitigate against future thrombosis.

Non-Factor Therapies for Hemophilia

The three non-factor therapies include the FDA-approved bispecific monoclonal antibody FVIII mimetic, emicizumab,[1,2] and inhibitors of clot regulators, including the siRNA antithrombin knockdown, fitusiran, [3] and the anti-tissue factor pathway inhibitors (anti-TFPI) befovacimab, concizumab, and marstacimab.[4, 5]

The mechanism of emicizumab hemostasis is by binding to factors IXa and X to mimic factor VIII coagulant function, activating coagulation through FIXa and FX, with progressive generation of thrombin[6] to promote hemostasis and reduce bleeds in those with hemophilia A with or without inhibitors.[1,2] This represents the first time an effective alternative to bypass therapy has been available for hemophilia A inhibitor patients. Given subcutaneously, emicizumab provides simpler administration, greater efficacy, and better quality of life than possible with standard FVIII or FVIII bypass therapy, e.g. rFVIIa or activated FIX (aPCCs).[1,2,7]

The second novel non-factor agent, fitusiran, currently in clinical trials, is a silencing RNAi that interferes with antithrombin (AT) mRNA translation and subsequent AT synthesis in the hepatocyte.[8] Knockdown of AT removes a major regulator of thrombin clot formation, allowing thrombin generation to continue unchecked and ongoing bleed reduction in individuals with hemophilia A or B, with or without inhibitors.[3,9] Moreover, this is the first time a potential therapy has been available for hemophilia B inhibitor patients that, not only by simpler monthly subcutaneous administration, but also with significantly better efficacy than standard bypass with rFVIIa or activated FIX (aPCCs), while avoiding potential life-threatening allergic reactions and anaphylaxis with the latter.[3,9,10]

The third group of non-factor therapies are monoclonal antibodies directed against tissue factor pathway inhibitor (TFPI), the major regulator of the initiation of coagulation,[11] and have been evaluated in early phase

clinical trials.[5,12] These include concizumab, a humanized IgG4 monoclonal antibody directed against the Kunitz 2 domain of TFPI,[13] marstacimab, a human IgG1 directed against the Kunitz 2 domain of TFPI,[14] and befovacimab, BAY 1093884, an IgG2 monoclonal antibody that binds the Kunitz 1 and Kunitz 2 domains of TPFI.[15] These agents prevent breakdown of clot formation, promoting continued thrombin generation and, in clinical trials, have significantly reduced bleeds and factor use.[4]

Hemostasis and Bleed Reduction

The major impact of the non-factor agents on patients with hemophilia has been to reduce bleeding events, including the number of breakthrough spontaneous or traumatic bleeds, including joint bleeds. With emicizumab prophylaxis there were up to 79% fewer bleeds and an annualized bleed rate (ABR) of up to 2.9 in hemophilia A patients across all age groups, with and without inhibitors, when dosed weekly, biweekly, or monthly,[1,2,7] a substantial improvement compared with bypass therapy (rFVIIa or aPCC) in inhibitor patients, or with recombinant factor VIII in those without inhibitors. Further, for both groups, there was significantly lower factor or bypass therapy use, fewer hospitalizations, fewer bleeding complications, and improved quality of life.[1,2,7] Moreover, patients not previously able to undergo surgery could do so under coverage of clotting factor.[7]

Among hemophilia A or B patients with or without inhibitors receiving fitusiran, significant reduction in ABR was observed, along with a significant reduction in factor or bypass therapy.[3] The spontaneous and traumatic breakthrough bleeds that did occur with fitusiran were typically mild in severity. Further, there was a significant improvement in quality of life,[3] most notable in patients with inhibitors who historically have the poorest response to treatment, the least favorable clinical outcomes, and the lowest well-being of those with hemophilia.

Similarly, among hemophilia A and B inhibitor patients and hemophilia A patients without inhibitors receiving anti-TFPI (concizumab), significant reduction in ABR occurred, including spontaneous and traumatic bleeds, and joint and non-joint bleeds, and with that correspondingly reduced use of factor and bypass therapy.[4]

Re-Balanced Coagulation

The major hemostatic defect in patients with hemophilia A and B is deficient or defective factor VIII or IX, which results in insufficient thrombin generation to make an effective fibrin clot to stop bleeding.[16-18] By mimicking a missing clotting factor or inhibiting a regulator of clot formation, the novel non-factor agents may "re-balance" the pro-coagulant and anti-coagulant pathways to restore thrombin generation to individuals in whom thrombin generation is defective. It is recognized, however, that the effects of "re-balanced" coagulation may depend on the underlying coagulopathy. In patients receiving non-factor therapies, coagulation function may be less robust than with standard clotting factor. For example, although emicizumab mimics the hemostatic interaction of FVIII with FIXa and FX, it does not possess other important FVIII functions, such as its interaction with platelets and the vascular endothelium, which may be important in coagulation and coagulation regulation.[19]

Further, as non-factor agents *prevent* but do not *treat* bleeds, standard factor is still required to treat acute bleeds, trauma, or surgery. Standard clotting factor is generally infused less frequently, at lower intensity, and for shorter periods than when given alone, in those receiving non-factor

prophylaxis. The latter may, however, increase thrombin generation. In fact, thrombin generation and peak thrombin were shown to increase when rFVIIa or aPCCs were combined ex vivo with fitusiran,[20] and when rVIIa, aPCCs, FVIII, or FIX were combined in vitro with concizumab.[21] Thus, it is possible that the concomitant use of standard clotting factor with non-factor therapies may tip the coagulation balance toward thrombosis.

Thrombosis

The occurrence of arterial and venous thrombosis in patients with congenital bleeding disorders was unexpected. These thrombotic events during clinical trials of all three non-factor therapies underscore the fine line between hemostasis and thrombosis and the potential risk for thrombosis in individuals with hemophilia receiving both non-factor therapy and standard factor for acute bleeds. In hemophilia A patients receiving emicizumab, thromboembolism and thrombotic angiopathy occurred in a total of seven thrombotic events during an early phase trial (Table 1). These included three patients who developed thrombotic microangiopathy (TMA) after receiving APCCs >100 U/kg in 24 hours for acute breakthrough bleeds.[1] In addition, there were three venous and one arterial thrombosis, with the site and types of the remaining thromboses still under study.[5] Of the venous events, one was a saphenous vein thrombosis associated with aPCCs > 100 IU/kg/24 hour treatment of a joint bleed, one was a cavernous sinus thrombosis associated with aPCCs > 100 IU/kg/24 hr. [22, 23]

Table 1. Thrombotic Events Associated with Novel Non-Factor Therapies

Agent	Target	Thrombotic Events	Associated Events
Emicizumab	FIXa and X	7 Events	
		(3) Thrombotic microangiopathy	aPCCs > 100 IU/kg/day
		(1) Cavernous sinus thrombosis	aPCCs > 100 IU/kg/day
		(1) Saphenous vein thrombosis.	aPCCs > 100 IU/kg/day
		(1) Superficial thrombophlebitis	
		(1) Sinus vein thrombosis	
Fitusiran.	Antithrombin	5 Events	
		(1) Cerebral sinus thrombosis	Repeat FVIII, tobacco use
		(1) Spinal artery thrombosis	Spinal injury/vascular disorder
		(1) Atrial thrombosis	Repeat rFVIIa for joint bleeds
		(1) Cerebrovascular accident	Past DVT, diabetes, smoker
		(1) Cerebral infarct	Recent prostate cancer
Befovacimab	TFPI		
		3 Events	
		(1) Ischemic stroke, right PCA	D-dimer, FP_{1+2} detected
		(1) Retinal artery thrombosis	
		(1) CNS venous thrombosis	

aPCCs is activated prothrombin complex concentrate; rFVIIa is recombinant FVIIa; DVT is deep venous thrombosis; Befovacimab is an anti-TFPI, formerly BAY 1093884; PCA is posterior cerebral artery; CNS central nervous system; TFPI is tissue factor pathway inhibitor; FP_{1+2} is fibrinopeptide fragment 1+2.

Among patients treated with fitusiran, five thrombotic events were reported. These events included three arterial thromboses: cerebral infarct, cerebrovascular accident, and suspected spinal artery thrombosis; and two venous thromboses, including a cerebral sinus thrombosis and an atrial thrombus during early phase trials.[2,9,24] These occurred in association with repeated high dose FVIII or rFVIIa.[20, 22,24] Subsequent analyses also revealed that antithrombin levels below 20% were predictive of thrombosis.[25]

Of anti-TFPI monoclonal antibody recipients, thrombosis was observed with only befovacimab, BAY 1093884, the IgG2 monoclonal antibody that binds the Kunitz 1 and Kunitz 2 domains of TPFI.[4,5] These were three central nervous system thrombosis, two arterial, including a posterior cerebral artery thrombosis, retinal artery thrombosis, and one venous thrombosis. D-dimer and prothrombin fragment FP_{1+2} were detected with dose escalation, but no correlation was noted between these coagulation activation markers and occurrence of thrombosis.

Thrombosis Prevention Strategies

Given the association of thrombosis with higher doses of clotting factor, it would seem reasonable to adjust doses of concomitant hemostatic agents downward when used with non-factor therapy, specifically to the lowest effective dose for the shortest time. Additionally maintaining diaries and contacting care providers if repeated doses are needed, for careful monitoring. For those receiving fitusiran, avoiding antithrombin levels below 15-20% is also suggested.[25] As coagulation activation markers D-dimer and FP_{1+2} are increased in those without thrombosis, they do not predict absolute risk, and, thus, monitoring is not recommended. Thrombin generation increases when factor and non-factor agents are used together. However, the in vitro assay by which it is measured varies from patient to patient and across laboratories, and while individualized thrombin generation profiles have been used in managing patients,[18] thrombin generation has not been useful in monitoring individual thrombotic risk.

The contribution of individual risk factors, such as increasing age, obesity, hypertension, cardiovascular disease, smoking, or past thrombosis may be important to consider in clinical decision-making regarding use of novel non-factor agents. Whether patients who are considered for non-factor therapies should be screened for inherited or acquired hypercoagulability, e.g. factor V Leiden, prothrombin gene variant, protein C, protein S, antithrombin deficiency, and lupus anticoagulant, is not known. In addition to a careful baseline history for familial clotting, long-term monitoring for thrombotic events should be encouraged and a registry begun. In those with obesity, hypertension, cardiovascular disease or who smoke, and risk-benefit discussion should be presented to each patient, along with education regarding symptoms of thrombosis and careful monitoring for thrombosis.

Prospective clinical and bench studies will also be needed to provide better delineation of margins of safety for bleeding and clotting with the current and future non-factor therapies. Despite the benefits of rebalancing hemostasis with novel non-factor therapies for hemophilia, the potential risk of thrombosis and the fine regulation of the coagulation system are just beginning to be appreciated.

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