Seminars in Hematology 53 (2016) 20–27

Contents lists available at ScienceDirect

Seminars in Hematology

journal homepage: www.elsevier.com/locate/enganabound

Advances in the clinical management of inhibitors in hemophilia A and B

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ARTICLE INFO

Available online 27 October 2015

Keywords:
Hemophilia
Inhibitors
Bypassing therapy
Acute bleeding
Immune tolerance induction
Prophylaxis

ABSTRACT

Inhibitors to factor (F)VIII or FIX are the most serious and challenging complication of hemophilia treatment, increasing morbidity and mortality because bleeds no longer respond to standard clotting factor replacement therapy. For patients with high-titer inhibitors, immune tolerance induction achieved through regular factor exposure is the only proven therapy capable of Inhibitor eradication and is almost always indicated for inhibitors of recent onset. Bypassing therapy is used to treat and prevent bleeding, but neither of the two currently available bypassing agents has the predictable hemostatic efficacy of factor replacement in hemophilia patients without inhibitors. Major research efforts are focused on the development of new, more potent therapies for the management of patients with inhibitors.

1. Introduction

Inhibitors are IgG antibodies that react with and bind to functional domains on the factor (F)VIII or FIX molecule, neutralizing its coagulant activity [1,2]. Approximately 30% of patients with severe hemophilia A [3] (baseline FVIII activity $<1\%$ of normal) develop inhibitory alloantibodies following exposure to clotting factor replacement therapy. Most FVIII inhibitors arise early in life (median age, 1.7–3.3 years), with the majority occurring between 10–20 exposures days [4,5]. Inhibitors to FIX are uncommon, developing in approximately 3% of patients with severe hemophilia B [6].

Inhibitors are considered the most serious complication associated with the treatment of hemophilia. Although the presence of an inhibitor does not generally change bleed site or frequency, it makes bleeding episodes more difficult to control because patients no longer respond to standard doses of clotting factor replacement therapy [7]. As a result, compared with hemophilia patients without inhibitors, inhibitor patients experience more severe joint disease and disability, owing to repeated, poorly controlled hemarthroses, and are at greater risk for life-threatening bleeds, such as intracranial hemorrhage, soft tissue bleeding, compartment syndrome, and post-procedure hemorrhage. Furthermore, necessary surgeries are often avoided because of the difficulty in predictably achieving hemostasis with current treatments [8,9] Collectively, these consequences of inhibitor development significantly reduce health-related quality of life (HRQoL) [10].

The presence of inhibitors also increases mortality risk. A recent multivariable analysis of data collected by the Centers for Disease Control and Prevention determined that the odds of death were 70% higher among patients with a current inhibitor compared with those without an inhibitor ($P<.01$) [11]. Additionally, deaths associated with inhibitors were considerably more likely to be attributed to bleeding complications: 42% versus 12%, respectively ($P<.0001$).

2. Inhibitor etiology, diagnosis, measurement, and classification

A variety of genetic and environmental factors are implicated in the development of inhibitors in patients with hemophilia, the most important being hemophilia gene mutation, race and ethnicity, and a family history of inhibitors [12–16]. Other well-recognized risk factors are listed in Table 1. Whether highly purified, recombinant (r) clotting factor concentrates are more immunogenic than plasma-derived (pd) concentrates, particularly those containing both FVIII and von Willebrand factor (FVIII/VWF) remains a subject of debate. An ongoing international trial that randomized children with newly diagnosed severe hemophilia A to receive rFVIII or pdFVIII/VWF has completed enrollment and may soon resolve this issue [17].

An inhibitor should be suspected whenever a bleeding event is not promptly controlled by the patient's usual replacement dose of clotting factor concentrate (CFC), or when breakthrough bleeding increases in a patient receiving prophylaxis. Occasionally, an inhibitor is detected on routine laboratory screening performed during a patient's clinic visit.

Inhibitors are quantified by the Bethesda assay, in which normal pooled plasma (a source of FVIII/FIX) is incubated with undiluted patient plasma for 2 hours at 37° C and assayed for residual FVIII/FIX [1]. One Bethesda unit (BU) is defined as the

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http://dx.doi.org/10.1053/j.seminhematol.2015.10.008
0037-1963/$/© 2016 Published by Elsevier Inc.

Table 1
Genetic and environmental risk factors associated with inhibitor development.

Genetic risk factors	Environmental risk factors
Hemophilia severity [12]	Intensive FVIII exposure (particularly early in life) [5,94]
Family history of inhibitors [13,14]	Immunologic/inflammatory/infectious events (ie, vaccination, surgery, illness) [5,95]
*F8/F9*genotype [12] • *F8* nonsense mutations, intron 22 and intron 1 inversions • *F9*: missense mutations and nonsense mutations	
Immune response genes • MHC [12,96] • Polymorphisms in cytokine genes (eg, TNFA, IL-10, CTLA-4 [97-99]	
Race/ethnicity (African or Latino descent) [15,16]	

MCH, major histocompatibility complex; TNFA, tumor necrosis factor alpha; IL-10, interleukin-10; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

amount of inhibitor needed to inactivate 50% of FVIII/FIX in pooled normal plasma. The sensitivity and specificity of the Bethesda assay is improved with the Nijmegen modification, wherein normal pooled plasma is buffered, and the imidazole buffer is replaced with inhibitor-free FVIII-/FIX-deficient plasma [18].

Inhibitors are classified as high-responding or low-responding on the basis of the rise in the Bethesda titer after exposure to clotting factor concentrates (ie, anamnestic response) [7]. High-responding inhibitors are defined by a peak inhibitor titer exceeding 5 BU and account for approximately 80% of all anti-FVIII or anti-FIX alloantibodies [19]. High-responding inhibitors are usually permanent unless eradicated via immune tolerance induction (ITI) [7]. Low-responding inhibitors measure ≤ 5 BU [20], are not anamnestic [20], and may be transient [7].

Once an inhibitor develops, clinical management is divided into 3 distinct categories (listed in order of importance): (1) treatment of acute bleeding, (2) inhibitor eradication through ITI, and (3) prevention of bleeding, especially in patients who have failed ITI or who have long-term inhibitors.

3. Treatment of acute bleeding

In patients with low-responding inhibitors, bleeding can usually be successfully controlled with large doses of CFCs to overwhelm the inhibitor and achieve measurable clotting factor levels. Bleeding in patients with high-titer, high-responding inhibitors is treated with factor concentrates known as “bypassing” agents, named for their ability to bypass the specific missing coagulation factor.

Two bypassing agents are currently available: activated prothrombin complex concentrate (aPCC) and recombinant activated factor VII (rFVIIa) (Table 2). These bypassing agents generate thrombin in the absence of FVIII or FIX through differing mechanisms of action) and also vary with regard to their pharmacokinetics. aPCC primarily targets the prothrombinase complex, augmenting the conversion of prothrombin to thrombin by FXa [21], and has a functional half-life of 4–7 hours [22]. rFVIIa activates sufficient FX on activated platelets to restore platelet surface thrombin generation [23], and its half-life is about 2 hours.[24

In clinical use, aPCC and rFVIIa control approximately 80% of acute bleeding episodes and have similarly low rates of adverse events [25–27]. However, substantial interpatient variability in response to treatment has been described by physicians and patients and was observed in the randomized, crossover FENOC trial, in which 30% of the study subjects reported that one bypassing agent was more effective than the other in the treatment of joint bleeding [27]. Moreover, some cases of severe or protracted bleeding fail to resolve with aPCC or rFVIIa monotherapy. In these situations, the sequential use of both bypassing agents may be necessary [28]. Although this strategy has generally been found safe and effective, it is an intensive therapeutic approach that requires hospitalization for careful monitoring.

For patients with high-responding inhibitors whose inhibitor titers fall below 5 BU, which may occur when they are not exposed to the offending FVIII/FIX antigen for some period of time (months to years), major or life-threatening bleeding may transiently respond to large doses of CFCs [29]. The duration of hemostatic efficacy is typically limited to 4–7 days, at which point anamnesis occurs, the high-titer inhibitor returns, and bypassing therapy must once again be used to control bleeding.

3.1. Adjunctive antifibrinolytic therapy

In severe hemophilia, compromised thrombin generation slows coagulation and results in clots that are vulnerable to fibrinolysis [30]. Abnormal thrombin generation also delays and reduces activation of FXIII and thrombin-activated fibrinolysis inhibitor (TAFI), further contributing to reduced clot stability [30]. Adjunctive antifibrinolytic therapy with tranexamic acid (TXA) or epsilon aminocaproic acid (EACA) is used empirically in hemophilia, primarily when there is a risk of mucosal bleeding, such as with dental procedures, to prevent clot degradation by plasmin. A recent study demonstrated that either bypassing agent plus oral TXA induced a significant increase in maximum clot firmness when compared with a bypassing agent alone, and the clot was indistinguishable from those of normal controls treated with TXA [30]. Concerns about an increased risk for thrombosis and DIC associated with concomitant bypassing and antifibrinolytic therapy have not been validated in clinical practice.

Table 2
Bypassing therapy for acute bleed management [21-27].

Parameter	aPCC	rFVIIa
Contents	FII (prothrombin), FVII, FIX, FX	rFVIIa
Mechanism of action	Targets prothrombinase complex	Activates FX on activated plateletsMechani
Half-life	4–7 hours	~2 hours
Dose/frequency	50–100 U/kg every 6–12 h, not to exceed • 100 U/kg per dose • 200 U/kg per day	90 μg/kg every 2 h 270 μg/kg*

* Clinical trial data showed single large dose of rFVIIa was as safe and effective as three smaller doses [100].