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Introduction to a Review Series on New Therapeutics for Inherited and Acquired Bleeding Conditions

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The management of patients with bleeding disorders is rapidly evolving, with the introduction of multiple new therapeutic options that improve or replace existing treatment modalities. The increasing number of options available to treat patients with inherited as well as acquired bleeding disorders is enabling the development of approaches that can be tailored to best fit the individual patient's unique needs. From the days when fresh frozen plasma and cryoprecipitate were the primary replacement therapies available to us, we are rapidly entering an era of precision medicine when it comes to the management of patients with bleeding disorders. This review series includes five articles that address new therapeutic options for patients with hemophilia, rare inherited bleeding disorders, and bleeding complications encountered by patients on anticoagulant therapies (Table).

Weyand and Pipe open the series by describing the explosion of new therapies for patients with hemophilia. Novel bioengineered factor VIII and factor IX molecules have been developed that exhibit extended circulating half-lives, as well as potentially decrease the development of factor inhibitors. Strategies for oral delivery of coagulation proteins are being explored as an approach to facilitate tolerance. Thinking outside the box of simply replacing what is missing, exciting recent developments include the approval of emicizumab as a "substitution therapy" for patients with factor VIII deficiency, and strategies that modulate natural anticoagulant mechanisms to offset the bleeding tendency associated with a specific coagulation factor deficiency, referred to as "hemostatic rebalancing".

Nogami and Shima extend upon the first review, providing more details concerning the non-factor products that are now available or in development for patients with hemophilia. Emicizumab, a bispecific monoclonal antibody, substitutes for factor VIIIa to provide a bridge between the enzyme, factor IXa, and its substrate, factor X. While providing effective hemostasis, it introduces unique challenges concerning therapeutic monitoring in the clinical laboratory as well as the development of safe approaches to treat breakthrough bleeding

events. Rebalancing hemostasis by modulating antithrombin expression with fitusiran, a small, interering RNA (*si*-RNA), leads to a decrease in bleeding complications in patients with hemophilia. Similarly, concizumab is a monoclonal antibody that binds to tissue factor pathway inhibitor, removing a block on the initiation of coagulation at the level of factor VIIa/tissue factor that can decrease hemorrhagic complications in patients with hemophilia.

Hemophilia has long been considered a disorder that should be amenable to gene therapy, and there have been impressive advances here over the last few years. Perrin, Herzog, and Markusic provide an update on this topic. In contrast to the other treatments for patients with hemophilia, gene therapy holds the prospect of a lasting cure with a single “dose” of therapy. Advances in the vectors and the expression cassettes have been designed to optimize targeting the liver and obtaining optimal expression levels of active factor in the circulation. The use of a factor IX sequence that encodes a hyperactive protein (factor IX Padua) has also been used in an effort to increase factor expression levels. Approaches to minimize toxicities continue to be explored, as do alternatives for patients with pre-existing immunity to the viral capsid being used for gene transfer.

Menegatti and Peyvandi provide an update on the treatment of rare factor deficiencies other than hemophilia. Deficiency of coagulation factors other than factor VIII and factor IX are much less common, and the development of new therapies specifically for patients with these factor deficiencies have lagged behind the introduction of new treatments for patients with hemophilia. Specific factor replacement therapies are available for patients with deficiencies of factor VII, factor XIII, and fibrinogen, but patients with deficiency of factors II, V, X, and XI are still dependent on the use of fresh frozen plasma, or, for patients with deficiencies of the vitamin K-dependent factors II or X, prothrombin complex concentrates. A potential benefit of the development of strategies designed to rebalance hemostasis for patients with hemophilia is that

these approaches may also prove to be beneficial for some of these patients with much less common bleeding disorders.

Finally, the management of bleeding complications developing in patients on anticoagulant therapy for thrombotic disorders has also seen the development of new therapies that can target specific anticoagulants. Piran and Schulman review the approaches to treat patients on different anticoagulants with hemorrhagic complications. Four-factor prothrombin complex concentrates are effective to rapidly reverse the anticoagulant effect of warfarin, similar to their efficacy in patients with inherited deficiency of vitamin K-depended factors. Therapies that can specifically reverse the direct oral anticoagulants include idarucizumab, a monoclonal antibody that targets the direct thrombin inhibitor dabigatran, and andexanet alfa, an inactive form of factor Xa that serves as a 'decoy' to bind and sequester the factor Xa inhibitors. Thromboembolic complications have occurred in some patients receiving these antidotes, reflecting the underlying prothrombotic risk that is still present when the anticoagulant is removed. These new therapies need to be integrated into the overall management of patients with an underlying thrombotic predisposition who have developed a hemorrhagic event related to their therapy.

These articles demonstrate how our understanding of fundamental mechanisms of normal hemostasis can be used to develop novel therapies that have a profound effect on the treatment of patients with a wide variety of bleeding disorders.

Table. A review series on new therapeutics for inherited and acquired bleeding conditions.

Authors	Title
Angela Weyand and Steven W. Pipe	"New Therapies for Hemophilia"
Keiji Nogami and Midori Shima	"New Therapies Using Non-Factor Products for Patients with Hemophilia and Inhibitors"
George Q. Perrin, Roland W. Herzog, and David M. Markusic	"Update on Clinical Gene Therapy for Hemophilia"
Marzia Menegatti and Flora Peyvandi	"Treatment of Rare Factor Deficiencies Other than Hemophilia"
Siavash Piran and Sam Schulman	"Treatment of Bleeding Complications in Patients on Anticoagulant Therapy"

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