

ABSTRACT FORM ECAT SYMPOSIUM 8 – 9 NOVEMBER 2018

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Title:

New Developments in Hemophilia Treatment

Abstract:

Since the mid-1960s, the treatment of hemophilia has comprised protein replacement therapy with clotting factor concentrates derived from either donated plasma or, since the 1990s, from recombinant DNA technology. Overall, these therapies are now safe and effective but still limited by a number of factors including the requirement for frequent intravenous administration, the development of neutralizing antibodies in 30% of hemophilia A patients, and the cost of these products.

Over the past decade, we have seen the pre-clinical development and now clinical introduction of a range of hemophilia therapies that do not rely upon protein replacement. There is every indication that these novel treatments will significantly change the landscape for hemophilia management over the next decade.

Two strategies are being used to treat hemophilia through non-factor replacement approaches. The first of these approaches uses a FVIII mimetic bispecific antibody, emicizumab, to partially reconstitute the tenase complex in hemophilia A patients. The treatment is administered by subcutaneous injection and can be delivered between once a week to once a month. Importantly, in addition to its benefit in regular hemophilia A patients, the therapy is also effective in patients with FVIII inhibitors. The development of anti-drug antibodies against emicizumab appears to be minimal, and apart from rare thrombotic complications when co-administered with FEIBA in FVIII inhibitor patients, the product appears free of complications.

The second non-factor replacement strategy involves several approaches to rebalance hemostasis through interference with one of the anticoagulant protein mechanisms. Furthest along in clinical evaluation is a small inhibitory RNA (siRNA) therapy to reduce antithrombin production (fitusiran), but other strategies to inhibit activated protein C (with a novel APC serpin) and tissue factor pathway inhibitor (using TFPI antibodies) are also under investigation and have, in some instances reached early phase clinical trial assessment.

Lastly, after three decades of basic and pre-clinical development, hemophilia gene therapy is now entering the phase of human clinical trial analysis. Several phase 3 clinical trials of both factor VIII and factor IX gene transfer will be conducted over the next 2-3 years. All of these studies utilize adeno-associated viral (AAV) vectors delivering clotting factor transgenes to the liver. To date, aside from episodes of vector dose-related transient hepatotoxicity, these therapies appear safe, and clotting factor levels of between 5-200% have been achieved that persist for up to 8 years.