Since the mid-1960s, the standard of care for hemophilia has comprised protein replacement therapies using either plasma-derived or recombinant concentrates. In the past 25 years following the catastrophe of widespread viral transmissions in the mid-1980s, hemophilia therapy has been safe and effective, and regular prophylactic schedules of treatment are being used in many countries around the world. Nevertheless, protein replacement therapy still has limitations. Treatment has to be administered through intravenous infusion, approximately 30% of hemophilia A patients develop neutralizing antibodies to their treatment, and the cost of therapy significantly limits access in the developing world. In this context, there have been significant efforts to develop new, more convenient and even safer treatments during the past decade. The first of these innovative approaches for hemophilia care are now entering the clinic.

New treatments for hemophilia can be classified into three major categories: bioengineered protein replacement therapies, non-replacement treatments and gene therapy.

The initial goal of new therapies for hemophilia has been to extend the half-lives of the proteins to reduce the frequency of intravenous infusions. This has now been achieved through a range of strategies including immunoglobulin Fc fusions and albumin intravenous infusions. This has now been achieved through a range of strategies including immunoglobulin Fc fusions and albumin intravenous infusions. The first of these innovative approaches for hemophilia care are now entering the clinic.

Immunogenicity does not seem to be a problem, and the convenience of the modified FIX products is, in particular, clearly enhancing the quality of life of many hemophilia B patients. Simultaneous with the advances in the development of enhanced forms of clotting factor concentrates, progress with the two non-replacement strategies for hemophilia therapy has also been significant. First to reach the clinic has been a bispecific humanized antibody (ACE910/Emicizumab®) that acts as a partial FVIII mimetic. This molecule provides some of the scaffold cofactor activity of FVIIIa in juxtaposing FIXa and FX to facilitate FXa generation.

There are several clear benefits of this molecule: it can be administered subcutaneously, has a prolonged therapeutic half-life (~20-25 days) and is functional in the presence of FVIII inhibitors. Recent phase 3 studies in adults and children with FVIII inhibitors have demonstrated dramatic reductions in bleeding events when emicizumab is administered in a weekly subcutaneous prophylaxis schedule. Results of two additional trials of emicizumab in non-inhibitor hemophilia A patients, and with monthly administration are keenly anticipated. During the adult phase 3 inhibitor study there were five severe adverse thrombotic events (three thrombotic microangiopathies and two venous thromboses) but all of these events occurred with the coincident administration of an activated prothrombin complex concentrate, a treatment combination that might plausibly be expected to result in an enhanced risk of thrombotic complications.

The second area of development has been the generation of several “hemostasis rebalancing” strategies aimed at inhibiting anticoagulant pathways in hemophilia and thus correcting the hemostatic imbalance caused by FVIII or FIX deficiency. The most advanced of these strategies has been the application of a small inhibitory RNA (siRNA)-mediated strategy to reduce antithrombin levels. This molecule (Fitusiran), can be administered subcutaneously, has a therapeutic half-life of ~3 weeks. Recent phase 1/2 clinical trial results suggest that reduction of antithrombin levels by ~75% can boost thrombin generation into the low end of the normal range in persons with
severe hemophilia. Additional rebalancing strategies are underway aiming to neutralize the activities of the tissue factor pathway inhibitor with antibody-mediated approaches and to neutralize activated protein C with a novel serine protease inhibitor.

The final area of therapeutic innovation that is now approaching the initiation of the first phase 3 clinical trials in humans is gene therapy. After three decades of pre-clinical development, AAV-mediated approaches to hemophilia gene therapy have now shown substantive benefits in several small phase 1/2 clinical trials. For hemophilia B, use of a gain-of-function FIX Padua transgene has recently enabled persistent FIX activity levels of ~30% to be generated for >1 year following intravenous delivery of a novel AAV vector. Effective gene transfer for FVIII has proven to be more challenging, however, the first clinical success has now been reported using high doses of an AAV5 vector and the concomitant transient administration of steroids. One year after administration, patients treated with this vector had persistent FVIII levels of 20-200% and their bleeding rates had been dramatically reduced.

These are remarkable times for the translation of innovative therapeutic strategies for hemophilia into the clinic. Within the next 5-10 years, the treatment landscape for this condition will very likely be radically different to that of the past 50 years (Figure 1). The wide range of new therapeutic approaches will require clinicians to give considerable thought in matching individual patients to specific treatment options. In addition, there should now be ample opportunities to extend the reach of effective hemophilia care to regions of the world that have previously been unable to afford protein replacement therapies. The advances in hemophilia therapy that have been achieved over the past decade are indisputable, and stand as a superb example of how investments in molecular science can dramatically enhance disease management.

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Figure 1. The therapeutic landscape for severe hemophilia A for the next five years. The options for treatment of hemophilia will significantly increase in number and diversity over the next few years. Depending upon a range of considerations – e.g. patient choice, regulatory approval and economic capacity – prophylactic treatment schedules should be accessible for increasing numbers of persons with hemophilia worldwide. PEG, polyethylene glycol; AT, antithrombin; siRNA, small inhibitory RNA; TFPI, tissue factor pathway inhibitor; Abs, antibodies; APC, activated protein C; serpin, serine proteinase inhibitor; Ig, immunoglobulin.
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