Making friends out of foes: novel therapeutic approaches for haemophilia

Catriona Mactier[1], Cedric Hermans[2]

[1]*Great Ormond Hospital for Children NHS Trust Haemophilia Centre, London, United Kingdom;*
[2]*Division of Haematology, Haemophilia Centre, Saint-Luc University Hospital, Université catholique de Louvain (UCLouvain), Brussels, Belgium*

Dear Sir,

The currently most promising treatments of haemophilia are gene therapy based on inactivated viral vectors and immunotherapy using a bispecific antibody mimicking the catalytic action of factor VIII (FVIII). Considering the past viral contamination of the haemophilia community and the persistent unavoidable and challenging development of neutralizing antibodies mainly against exogenous FVIII, it was not expected that viral vectors and antibodies would serve to develop and validate treating or curing approaches for patients with haemophilia.

Infectious complications have historically been a major issue in the treatment of patients with haemophilia (PWH). Thousands of PWHs were infected with bloodborne viruses such as HIV, Hepatitis B and C in the 1970s and 1980s[1]. There have been significant improvements in factor replacement therapy with the development of plasma-derived products with multiple viral inactivation steps and recombinant coagulation factor concentrates of increasing purity[2]. Both treatment modalities are nowadays generally considered "safe" with respect to the risk of transmitting infectious agents. Nevertheless, the residual, albeit very low level, risk of infection transmission with plasma-derived products has led to controversy and variable clinical practice across the world, particularly with the possibility of emerging unknown infections. In spite of all these developments, virus agents and their transmission by transfusion are still perceived by the haemophilia community as a major threat. This explains why recombinant products have largely or exclusively been adopted as replacement therapies in many countries[3].

While viruses should no longer negatively affect the haemophilia community, modified viruses used as vectors for gene therapy are now receiving major attention. Over the last *10 years*, gene therapy has been developed to treat haemophilia. Severe Haemophilia B (SHB) and, more recently, severe Haemophilia A (SHA) patients have both been successfully treated in trials[4]. An adeno-associated viral vector is used to introduce the missing gene (FVIII and FIX in SHB and SHA respectively) into the liver cells of the recipient, resulting in the production of the missing clotting factor. The virus is modified to avoid infection in the patient. The main side effect is associated with development of an immune response to the viral vector, which is managed with steroids. The results have been impressive with increased factor levels and a significant reduction in bleeding episodes and clotting factor usage, even sometimes completely. The longevity of the response and potential for "cure" remains to be established[5].

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Correspondence: Cedric Hermans
E-mail : cedric.hermans@uclouvain.be

The development of inhibitors to exogenous FVIII, and less commonly FIX, is an ongoing issue and one of the biggest challenges in modern-day haemophilia management. Approximately 15-30 % of SHA patients will develop an inhibitor[6]. The production of clotting factors by human cells line and their modification by different strategies (pegylation, Fc fusion, albumin fusion) could potentially influence the immunogenicity (speculation at this stage). There has been significant progress in immune tolerance induction, with emerging data showing that even adults with longstanding inhibitors may achieve tolerance[7]. However, a minority of cases will have a persistent inhibitor. In spite of these changes, the development of allo-antibodies against exogenous FVIII is a much-feared complication, in particular by parents with a young child starting replacement therapy. Management of these patients is challenging. Until recently the only available treatments were bypassing agents, namely plasma-derived activated prothrombin complex concentrate (aPCC) or recombinant activated factor seven (rFVIIa). There are no reliable laboratory tests to assess accurately response to bypassing agents and correction of haemostasis may be incomplete.

While this risk persists, a bispecific antibody mimicking FVIIIa has recently been developed. Emicizumab is a monoclonal bispecific antibody delivered once-a-week or less frequently. It binds two epitopes, on activated factor IX (FIXa) and factor X (FX), imitating the function of co-factor activated FVIII[8] . This novel antibody therefore overcomes the adverse nature of alloantibodies to FVIII. Main side effects include reactions at injection sites and a risk of thrombotic complications related to concomitant use of aPCC. Emicizumab has also been evaluated (Haven 4) for long term treatment in patients without inhibitor and could potentially be used in PUPs and avoid exposure to FVIII[9,10].

Viruses causing major infections and antibodies neutralizing FVIII represent the two major complications of haemophilia therapy over the last decades. While these 2 complications are now controlled or better managed, friendly viral vectors for the FVIII or FIX gene and antibodies not neutralizing FVIII but mimicking FVIII are now changing the short- and long-term management of haemophilia. The science behind these new approaches is complex, even for physicians. Initiatives should be encouraged so that patients understand the rationale for using viral vectors and antibodies to treat their bleeding disease. Those who live with chronic diseases, particularly rare ones, have been empowered to understand and manage their own condition. It is important that clear and relevant information is delivered to patients as innovative therapies develop, in good coordination with patient associations. Whilst this changing landscape is exciting, the degree to which these new strategies will be adopted into widespread clinical care will depend on accessibility, understanding and acceptance of these novel treatments by the wider community of haemophilia patients.

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