Non-replacement therapy for haemophilia treatment: fetching the east by the west

Marco Marietta[1], Mario Luppi[1,2]

[1]Haematology Unit, Azienda Ospedaliero-Universitaria di Modena, Italy; [2]Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy

Traditionally, historians date the beginning of the Modern Age as 1492, when Cristopher Columbus discovered America. This Italian sailor's innovative approach to reach the Indies was based on the idea of *buscar el levante por el poniente*, i.e. to fetch the east by the west.

The recently published review by Franchini and Mannucci[1] shows us that we are at the beginning of a modern age in the treatment of haemophilia, based on the same unconventional way to approach a problem.

Haemophilia is defined as "an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) (in haemophilia A) or factor IX (FIX) (in haemophilia B). The deficiency is the result of mutations of the respective clotting factor genes"[2].

The most logical approach to the treatment of a factor deficiency is to provide the patient with the lacking factor, either derived from human plasma, or produced by recombinant DNA technology. This approach has proven to be very effective and has substantially reduced morbidity and mortality in the haemophilia community: indeed, the life expectancy of people with haemophilia, which was around 57 years in the 1960s and 1970s in Sweden, is now matching that of the general population in high-income countries[3]. Moreover, prophylaxis has further improved the quality of life of people with haemophilia, preventing bleeds and subsequent haemophilic arthropathy and enabling participation in physical activities, with a substantial clinical benefit confirmed also by a Cochrane systematic review[4].

Despite its efficacy, prophylaxis is not able to meet all the needs of haemophilia patients, as frequent intravenous infusions of the lacking factor are required in order to maintain a trough level >1%. Moreover, in a relevant percentage of patients with haemophilia A the replacement therapy with factor concentrates is associated with the development of polyclonal neutralising IgG4 antidrug antibodies (inhibitors) to factor VIII, which negatively affect the efficacy of the haemostatic treatment, leading to patients with inhibitors having a worse outcome compared to those without inhibitors.

Various approaches have been used in order to overcome these obstacles to replacement therapy, including increasing the half-life and reducing the immunogenicity of infused recombinant factors. The latest generations of recombinant factors VIII and IX, including those with extended half-lives, have led to some improvements with respect to these issues, more relevant as far as haemophilia B treatment is concerned, but they have not eliminated either the need for repeated intravenous infusions, or the risk of inhibitor development[5].

Gene therapy is based on the same conceptual approach, although more advanced. Several years ago, in a very nice review published in the New England Journal of Medicine, Professor Mannucci wrote that "Haemophilia is likely to be the first common severe genetic condition to be cured by gene therapy […]. We can confidently predict that the new millennium will see an end to this ancient scourge"[6].

After two decades into clinical trial investigation, and five years after the first successful continuous expression of clotting factor, the great expectations about gene therapy have not been fulfilled. Indeed, despite the encouraging results of recently published clinical trials, the hope that gene therapy may finally solve the problem of haemophilia care still remains distant for the vast majority of patients[7,8].

But, as Columbus teaches us, there are many unconventional ways to solving a problem, based on so-called "lateral thinking". This expression was coined in 1967 by Edward de Bono to indicate an indirect and creative approach which uses not immediately obvious reasoning and involves ideas that may not be reached by traditional step-by-step logic. The development of non-replacement-based therapies for the treatment of haemophilia is an excellent example of such an approach.

Indeed, as reviewed by Franchini and Mannucci[1], many strategies have been developed recently to overcome the defect in coagulation caused by the lack of a single factor. These strategies differ from each other as far as the target of intervention is concerned, but all share the common idea of activating the haemostatic response in an alternative way, i.e., by replacing the co-factor function of factor VIII as in the case of emicizumab[9,10] or by altering the balance of pro- and anticoagulant

*Blood Transfus 2018; **16**: 408-9* DOI 10.2450/2018.0032-18

proteins. The latter is the case of concizumab, which blocks the activity of tissue factor pathway inhibitor[11], of fitusiran, which reduces antithrombin acitivity in a dose-dependent manner[12], as well as of the very recently developed serpin specific for activated protein C[13] or protein S silencing RNA[14].

The non-factor replacement strategies or "disruptive therapies" have exciting potential for haemophilia patients, particularly those with inhibitors, who can also hope for an innovative approach to immune-tolerance therapy by engineered chimeric T-cell antigen receptor technology[15].

If the preliminary results of the published trials are confirmed, these products could revolutionise the daily management of patients with inhibitors and provide a more convenient alternative for those without inhibitors.

What does this mean from the patients' perspective, and what from that of physicians?

Haemophilia patients, irrespective of whether or not they have inhibitors, can realistically hope for a substantial change in their quality of life in the next few years, because all these innovative treatments share a subcutaneous route of administration, greatly reducing treatment burden. Indeed, both patients and investigators involved in phase III clinical trials with emicizumab already enthusiastically report on a dramatic improvement in the patients' everyday quality of life.

Some issues, such as the long-term safety and the costs of these innovative strategies, as well as the problem of how (and if) to monitor treatment with non-clotting factor therapies require further and careful assessments. Nevertheless, the perspective of treating haemophilia simply with one subcutaneous injection a week and having a zero-annual bleeding rate is no longer just a dream.

Physicians involved in haemophilia care have an exciting opportunity for refining and improving their way of thinking about the organisation of Haemophilia Centres, accepting the idea that in a period of less ten years, at least in high-income countries, the everyday treatment of haemophilia will not be substantially different from that of other chronic diseases, such as diabetes. However, even in this mutated scenario the role of Haemophilia Centres will remain crucial, as these centres offer the due clinical competence to assist haemophilia patients as well as healthcare system providers in choosing the most appropriate drug for every single patient, in a perspective of a highly individualised haemophilia care, such as that required by precision medicine.

The Authors declare no conflicts of interest.

References

1) Franchini M, Mannucci PM. Non-factor replacement therapy for haemophilia: a current update. Blood Transfus 2018; **16**: 457-61.
2) Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al; Treatment Guidelines Working Group on Behalf of The World Federation of Hemophilia. Guidelines for the management of hemophilia. Haemophilia 2013; **19**: e1-47.
3) Payne AB, Ghaji N, Mehal J, et al. Mortality trends and causes of death in persons with hemophilia in the United States, 1999-2014. Blood 2017; **130** (Suppl 1): 755.
4) Iorio A, Marchesini E, Marcucci M, et al. Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B. Cochrane Database Syst Rev 2011; **9**: CD003429.
5) Mannucci PM, Franchini M. Present and future challenges in the treatment of haemophilia: a clinician's perspective. Blood Transfus 2013; **11** (Suppl. 4): s77-81.
6) Mannucci PM, Tuddenham EG. The hemophilias - from royal genes to gene therapy. N Engl J Med 2001; **344**: 1773-9.
7) Miesbach W, Meijer K, Coppens M, et al. Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia Blood 2018; **131**:1022-31.
8) Rangarajan S, Walsh L, Lester W, et al. AAV5-factor VIII gene transfer in severe hemophilia A. N Engl J Med 2017; **377**: 2519-30.
9) Shima M, Hanabusa H, Taki M, et al. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. N Engl J Med 2016; **374**: 2044-53.
10) Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med 2017; **377**: 809-18.
11) Chowdary P, Lethagen S, Friedrich U, et al. Safety and pharmacokinetics of anti-TFPI antibody (concizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial. J Thromb Haemost 2015; **13**: 743-54.
12) Pasi KJ, Rangarajan S, Georgiev P, et al. Targeting of antithrombin in hemophilia A or B with RNAi therapy. N Engl J Med 2017; **377**: 819-28.
13) Polderdijk SGI, Adams TE, Ivanciu L. Design and characterization of an APC-specific serpin for the treatment of hemophilia. Blood 2017; **129**: 105-13.
14) Prince R, Bologna L, Manetti M, et al. Targeting anticoagulant protein S to improve hemostasis in hemophilia. Blood 2018; DOI: 10.1182/blood-2017-09-800326.
15) Yoon J, Schmidt A, Zhang AH et al. FVIII-specific human chimeric antigen receptor T-regulatory cells suppress T- and B-cell responses to FVIII. Blood 2017; **129**: 238-45.

Correspondence: Marco Marietta
Haematology Unit
Azienda Ospedaliero-Universitaria di Modena
via del Pozzo 71
41124 Modena, Italy
e-mail: marco.marietta@unimore.it