HHS Public Access

Author manuscript

Br J Haematol. Author manuscript; available in PMC 2022 March 22.

Published in final edited form as:

Br J Haematol. 2021 September ; 194(5): 805–807. doi:10.1111/bjh.17661.

Haemophilia care: the only constant is change

Benjamin J. Samelson-Jones[1,2], **Lindsey A. George**[1,2]

[1]Division of Hematology and the Perelman Center for Cellular and Molecular Therapeutics, Children's Hospital of Philadelphia,

[2]Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Prior to modern medical care, haemophilia was a lethal paediatric disease[1] indeed, limitations in haemophilia care affected the political activity of the royal houses of Europe leading up to World War I in which multiple of Queen Victoria's descendants inherited haemophilia B and publicly succumbed to complications at a young age.[2] Fortunately, the advances in blood banking following World War II provided the first haemostatic treatments for people with haemophilia. As is comprehensively reviewed in this issue by Doctors Fassel and McGuinn[3], haemophilia treatment has subsequently evolved from this early use of whole blood and large volume plasma transfusions to increasingly sophisticated biotechnologies with two new therapeutic categories of extended half-life (EHL) factor products and non-factor therapies (NFTs), both receiving regulatory approval within the last decade. As they outline, innovation in haemophilia continues unabated with several new (and hopefully improved) EHL factor products and NFTs advancing rapidly through clinical development. The authors also discuss the multiple ongoing haemophilia gene therapy trials in various phases of clinical development, ranging from proof-of-concept studies to pivotal licensing trials for both haemophilia A and B. With this expanding and diverse therapeutic armamentarium, both clinicians and patients have begun contemplating what a functional cure of haemophilia might look like.[4]

The pace of progress of novel drug development for haemophilia combines two strengths of the field: 1) a depth of understanding in the molecular basis of the disease including the biochemistry of coagulation that permits rational design of new therapies, and 2) an organised patient advocacy and physician provider network that fosters both basic research and clinical trials. These attributes are further amplified by advances in molecular therapeutics, especially gene therapy, in which haemophilia has long been a targeted disease.[5] The rapidity of innovation may be fuelled, in part, by the high cost of current

Correspondence: Benjamin J. Samelson-Jones, University of Pennsylvania School of Medicine, Hematology, The Children's Hospital of Philadelphia, Colket Translational Research Building, Room 5028, 3501 Civic Center Boulevard, Philadelphia, PA 19104 USA. samelsonjonesb@chop.edu; Lindsey A. George, University of Pennsylvania School of Medicine, Director of Clinical In Vivo Gene Therapy, The Children's Hospital of Philadelphia Hematology, The Children's Hospital of Philadelphia, Colket Translational Research Building, Room 5016, 3501 Civic Center Boulevard, Philadelphia, PA 19104 USA. georgel@email.chop.ed.

Conflict of interest

Benjamin J. Samelson-Jones has been a consultant for Pfizer, Bayer, Genentech, Frontera and Cabaletta and serves on the Scientific Advisory Board of GeneVentiv. Lindsey A. George has been a consultant for Pfizer, Bayer, CSL Behring and serves on the Data Monitoring Committee Advisory Board of Avrobio. For both Benjamin J. Samelson-Jones and Lindsey A. George, fees are provided to The Children's Hospital of Philadelphia where they practice for study participation from Spark Therapeutics and Pfizer.

therapies that likely incentivise pharmaceutical interest and research. Early data suggest that some new therapies for haemophilia may modestly reduce the cost of therapy.[6] However to date, these novel therapies do not appear to have meaningfully decreased the treatment gap between patients in developed and developing countries, with most haemophilia patients worldwide continuing to have only limited or no access to haemostatic agents. Nonetheless, there is hope that new haemophilia therapeutics may decrease the market shares of some established drugs driving down pricing and expanding target markets and, consequently, treatment options for those patients that do not currently routinely have access to therapy.

As the authors review, how these new drugs will reshape haemophilia care and how best to implement them into clinical practice remain open questions, but there is considerable optimism. For example, the success of emicizumab, a bispecific antibody that indiscriminately binds factor IX (FIX)/activated coagulation FIX (FIXa) and FX/FXa mimicking FVIII's function to co-localise the protein components of the intrinsic tenase,[7,8] for prophylaxis of severe haemophilia A with and without inhibitors[9,10] has substantially 'de-medicalised' severe haemophilia A care.[11] In turn, the success of emicizumab has challenged the role of immune tolerance induction as a stalwart, standard of care for patients with haemophilia A with inhibitors and reduced care demands of haemophilia treatment centres.

The long-term success of the expansive repertoire of novel EHL factor products and NFTs recently licensed or in clinical development will be predicated on understanding their mechanistic basis and finding answers to outstanding questions emerging from clinical trials. For example, the development of NFTs have shown a series of thrombotic adverse events when combining the NFT under-study with other haemostatic therapies. Thrombotic complications were initially observed after emicizumab study participants were given multiple doses of activated prothrombin complex concentrate (aPCC) to treat break-through bleeding. Notably, emicizumab function is largely dependent on FIXa and infusion of exogenous sources of FIXa (present in aPCCs, wherein aPCC dosing is based on FIXa activity), at least in part, rationally explains this thrombotic complication of emicizumab that was perhaps predictable.[8] A subsequent mitigation strategy recommended limiting concomitant administration of emicizumab and aPCC to <100 u/kg/day, which has been mostly successful, although thrombotic complications have continued to be reported even after licensure.[12] Additionally, thrombotic complications were observed with concurrent FVIII administration in study participants receiving fitusiran, a small interfering RNA (siRNA) that inhibits antithrombin translation. The study sponsor is continuing the clinical development of fitusiran but has decreased the degree of the targeted antithrombin knock down. Likewise, a mitigation strategy with revised recommendations on concomitant guidelines for break-through bleeding was also implemented during the clinical development of a concizumab, a monoclonal antibody targeting tissue factor pathway inhibitor to reduce pro-thrombotic concerns. The safe and effective implementation of haemostatic regimens with multiple drugs will likely continue to be a challenge for haemophilia care.

Thus, while an understanding of *all* molecular interactions novel agents engage will optimise clinical adaptation, a suggested minimum threshold may be an understanding of the molecular basis of function to evaluate pro-thrombotic risk. For example, extensive

preclinical studies and biochemical characterisation of the gain-of-function FIX variant Padua used in all currently enrolling haemophilia B gene therapy trials were reassuring of its safety at normal FIX activity levels,[13,14] despite now a single report of a thrombotic complication in a gene therapy recipient with supratherapeutic FIX activity after vector administration and additional pro-thrombotic risk factors (obesity and renal failure).[15] Indeed, the demonstrated therapeutic advantage of using a gain-of-function transgene for haemophilia B gene therapy raises the question if a rationally designed gain-of-function FVIII mutation, of which there are multiple described, may similarly improve haemophilia A gene therapy efforts.[16,17]

Fassel and McGuinn also delineate the diverse gene therapy approaches in preclinical and clinical development for haemophilia A and B. Adeno-associated viral (AAV) vectors remain the most advanced, such that four vectors are now in phase III development and regulatory approvals are widely anticipated in the short term. Several alternative gene therapy strategies (e.g. cell-based therapies and *in vivo* gene-editing approaches) are also being investigated in phase I/II studies or progressing through preclinical development. Gene therapy has the potential to fundamentally alter haemophilia care with the goal that a single therapeutic administration may safely and predictably impart long-term phenotypic amelioration. However, all AAV vector recipients uniformly develop persistent, multi-serotype cross-reactive neutralising antibodies to AAV that currently likely prevent the efficacy of repeat AAV vector administration, regardless of serotype.[18,19] Thus, potential AAV recipients, either clinical trial participants or patients post-licensure, need to recognise that they will likely only receive a single AAV gene therapy in their lifetime with the current state of science. These considerations create a scenario for ‘buyer’s remorse’ in gene therapy recipients that get an AAV product that is subsequently found to be substantially inferior to a newer AAV vector. It is critical, therefore, that all clinical trial results (irrespective of success) are published with sufficient details to inform patients and clinicians, as well as aid translational and basic work to understand the multiple unanswered questions that have emerged from clinical trials.[20] Fassel and McGuinn identify several ongoing challenges for gene therapy in addition to the problems of the humoral immune response to AAV vector that include and span: potential for genotoxicity, long-term durability of expression that is of particular concern for haemophilia A, the role of immunomodulatory therapy, heterogeneity and, in some cases, unpredictable levels of transgene expression, lack of AAV neutralising antibody assay standardisation in which variable methods markedly affect results, and the role of gene therapy in the care patients with inhibitors for which preclinical studies support the ability of liver-directed gene transfer to induce tolerance.[14,21]

As is clear from Fassel and McGuinn’s review, the only constant in haemophilia care is that it will continue to advance. The breadth of new technologies currently in clinical development and in preclinical studies for the care of people with haemophilia will increasingly require physicians to thoughtfully and thoroughly understand the science behind these new treatment options. These novel therapeutics highlight the need for greater collaboration between scientists and clinicians to safely and efficiently incorporate these new therapies into clinical practice and work together to answer outstanding questions that have emerged from clinical trials.

References

1. Birch CL. Hemophilia, clinical and genetic aspects. Illinois Monogr Med Sci 1937;1:1–151.
2. Lannoy N, Hermans C. The 'royal disease'–haemophilia A or B? A haematological mystery is finally solved. Haemophilia. 2010;16:843–7. [PubMed: 20557352]
3. Fassel H, McGuinn C. Hemophilia: Factoring in New Therapies. Br J Haematol. 2021;194:835–50. [PubMed: 34322873]
4. Skinner MW, Nugent D, Wilton P, O'Mahony B, Dolan G, O'Hara J, et al. Achieving the unimaginable: health equity in haemophilia. Haemophilia. 2020;26:17–24. [PubMed: 31724316]
5. Mendell JR, Al-Zaidy SA, Rodino-Klapac LR, Goodspeed K, Gray SJ, Kay CN, et al. Current clinical applications of in vivo gene therapy with AAVs. Mol Ther. 2021;29:464–88. [PubMed: 33309881]
6. Samelson-Jones BJ, Guelcher C, Kuhn J, Butler R, Massey G, Guerrera MF, et al. Real-world cost estimates of initiating emicizumab in US patients with haemophilia A. Haemophilia. 2021 (Online ahead of print). 10.1111/hae.14347.
7. Kitazawa T, Igawa T, Sampei Z, Muto A, Kojima T, Soeda T, et al. A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model. Nat Med. 2012;18:1570–4. [PubMed: 23023498]
8. Lenting PJ, Denis CV, Christophe OD. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? Blood. 2017;130:2463–8. [PubMed: 29042366]
9. Oldenburg J, Mahlangu JN, Kim B, Schmitt C, Callaghan MU, Young G, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377:809–18. [PubMed: 28691557]
10. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med. 2018;379:811–22. [PubMed: 30157389]
11. McCary I, Guelcher C, Kuhn J, Butler R, Massey G, Guerrera MF, et al. Real-world use of emicizumab in patients with haemophilia A: bleeding outcomes and surgical procedures. Haemophilia. 2020;26:631–6. [PubMed: 32311809]
12. Ebbert PT, Xavier F, Seaman CD, Ragni MV. Emicizumab prophylaxis in patients with haemophilia A with and without inhibitors. Haemophilia. 2020;26:41–6. [PubMed: 31746522]
13. Samelson-Jones BJ, Finn JD, George LA, Camire RM, Arruda VR. Hyperactivity of factor IX Padua (R338L) depends on factor VIIIa cofactor activity. JCI Insight. 2019;4:e128683.
14. Crudele JM, Finn JD, Siner JI, Martin NB, Niemeyer GP, Zhou S, et al. AAV liver expression of FIX-Padua prevents and eradicates FIX inhibitor without increasing thrombogenicity in hemophilia B dogs and mice. Blood. 2015;125:1553–61. [PubMed: 25568350]
15. Chowdary P, Shapiro S, Makris M, Evans G, Boyce S, Talks K, et al. Late-breaking and COVID-19 oral communication session abstracts. Res Pract Thromb Haemost. 2020;4(Suppl 2):1–25.
16. Samelson-Jones BJ, Arruda VR. Protein-engineered coagulation factors for hemophilia gene therapy. Mol Ther Methods Clin Dev. 2019;12:184–201. [PubMed: 30705923]
17. Wilhelm AR, Parsons NA, Samelson-Jones BJ, Davidson RJ, Esmon CT, Camire RM, et al. Activated protein C has a regulatory role in factor VIII function. Blood. 2021;137:2532–43. [PubMed: 33512448]
18. George LA, Ragni MV, Rasko JE, Raffini LJ, Samelson-Jones BJ, Ozelo M, et al. Long-term follow-up of the first in human intravascular delivery of AAV for gene transfer: AAV2-hFIX16 for severe hemophilia B. Mole Ther J Am Soc Gene Ther. 2020;28:2073–82.
19. Long BR, Veron P, Kuranda K, Hardet R, Mitchell N, Hayes GM, et al. Early phase clinical immunogenicity of valoctocogene roxaparvovec, an AAV5-mediated gene therapy for hemophilia A. Mol Ther. 2021;29:597–610. [PubMed: 33309883]
20. Pierce GF, Kaczmarek R, Noone D, O'Mahony B, Page D, Skinner MW. Gene therapy to cure haemophilia: is robust scientific inquiry the missing factor? Haemophilia. 2020;26:931–3. [PubMed: 32909632]

21. Finn JD, Ozelo MC, Sabatino DE, Franck HW, Merricks EP, Crudele JM, et al. Eradication of neutralizing antibodies to factor VIII in canine hemophilia A after liver gene therapy. Blood. 2010;116:5842–8. [PubMed: 20876851]