Check for updates

Received: 6 August 2021 | Revised: 27 September 2021 | Accepted: 6 October 2021

DOI: 10.1111/hae.14440

Haemophilia WILEY

LETTER TO THE EDITOR

Implications of haemophilia gene therapy for the changing role of the multidisciplinary team

Gene therapies (GT) for haemophilia are in clinical trials, and under review by regulatory agencies with an expectation they may become available in clinical practice over the coming years. This new treatment modality represents a paradigm shift in care for people with haemophilia (PwH), and will have an impact on the traditional set up of haemophilia treatment centres (HTCs). A recent joint statement from EAHAD and EHC recommended that first-generation GT should be managed using a hub-and-spoke model, with GT prescribed and managed exclusively in expert comprehensive care centres (the hub), and monitored in HTCs (the spokes) in close communication.[1] We would like to examine the importance of engaging with the multidisciplinary team (MDT) across different centres, and examined how effective communication will support an individualised approach to care in the era of GT. The key to success will be collaboration, and members of the MDT have a shared responsibility in supporting the GT journey. There are several stakeholders in the MDT; here we consider the roles of the haematologist, nurse, physiotherapist, and psychologist based on our own experience, whilst acknowledging that there is heterogeneity in services across Europe and globally, which may affect the scope of individual roles.

The physician has a central or coordinating role in GT, and with shared care between hub and spoke centres it will need to be clear who is responsible for the GT recipient at each stage.[2] The physician in a spoke centre is responsible for initial communication with each candidate PwH regarding how GT works, and discussing possible clinical benefits and variability of results–as well as making decisions on eligibility and promoting a shared-decision making approach through access to centralised and unbiased sources of information.[3] This includes promoting awareness of inclusion and exclusion criteria in the GT clinical trials, such as the presence and significance of anti-AAV antibodies.[3,4] The spoke physician may attend the infusion at the hub to support the procedure, and take risk information back to the spoke HTC. Long-term follow-up and monitoring will take place back in the spoke HTC, where GT recipients should receive regular follow-up appointments, as well and ongoing advice and support around contraception, alcohol, and the potential need for steroids. However, there should be an ongoing relationship with the hub with regards laboratory results, adverse events, and adherence. Adverse events should be managed by both hub and spoke centres to provide timely and state-of-the-art treatment options and maximise long-term benefits.[1] All adverse events should be reported to a centralised scheme—including bleeding episodes.[1] Physicians in the hub will have differing roles—including welcoming transferred GT candidates and enabling facilities for optimal dosing—and orchestration of these roles requires coordination. Communication between a network of hub centres could help optimise GT over time.

Nurses within the MDT have a close relationship with PwH, and whilst this will remain unchanged, nurses may take on new tasks for GT candidates. One of the additional challenges may be to coordinate the patient journey and ensure that information is shared between the hub and spoke centres. In clinical trials for GT, nurses have been instrumental in screening, with a role in providing education and awareness about GT, and planning for follow-up monitoring and life changes. Survey data of patients in clinical trials show that the main fear is side effects, but also suggest that after discussing adverse events seen in clinical trials, 40% are confident to continue in the trial when their physician called them, 32% when they talked to nurses, and 28% when they discussed the issues with their physician in the hospital.[5] Pre-infusion, spoke nurses can identify doubts around issues such as contraception and longevity, and offer education and information to make the PwH's GT decision informed and safe.[3] Frequently asked questions focus on risks, factor levels, and hereditability of the modified gene. On the infusion day at the hub centre, where nurses may spend several hours with the GT recipient, staying close at hand for a variety of procedures and helping to explain each. With the advent of GT, all HTC nurses should know that potential GT risks include a strong immune system response, targeting the wrong cell, infection, and hepatic carcinoma—and be able to answer questions from PwH around these topics. Additionally, in some cases GT has resulted in factor levels well over the normal range, which may be associated with increased clotting risks—although no adverse effects have been reported to date. Working through a series of common questions with a nurse gives PwH the opportunity to make an informed choice about GT.[3,6] Managing expectations is an important part of the GT journey, and public opinion has been influenced by extensive media coverage, which may mean candidates perceive GT as a guaranteed life-long cure. Yet it remains unknown whether one-time infusion will be successful in the long-term, or if re-treatment will be needed

There is considerable heterogeneity in physiotherapy across Europe, with variance in roles and responsibilities, as well as access. Yet physiotherapists specialised in haemophilia play a crucial role in the care of PWH, and should be part of the standard MDT.[7] Physiotherapy will remain an important element after GT, even for PwH with little joint damage and limited risks. The role in the GT candidate

 © 2021 John Wiley & Sons Ltd.

Box: Core roles in supporting GT for PwH

Treating physician	Consider acceptable outcomes for each PwH regarding safety and efficacy Promote awareness of potential adverse events.[3]
Nurse	Manage expectations Support decision-making Coordinate cooperation and communication between the hub and spoke centres, and the PwH.
Physiotherapist	Continue to assess the risk of physical activities Perform musculoskeletal assessments
Psychologist	Pre-infusion assessment of potential dedication and compliance Resolve difficulties post-infusion, such as issues with identity or fear of losing expression over time

will include monitoring, musculoskeletal assessment and shared decision-making in the pre-infusion phase, as well as ongoing recommendations for suitable physical activity and sports, and management of existing arthropathy post-infusion. Physiotherapists spend a lot of time with each PwH, and understand their personality, aspirations, and difficulties, including limitation of activities and participation restrictions—elements that could be key in deciding eligibility for GT. Post-infusion, GT recipients will likely experience fewer bleeds, but may become less adept at recognising or handling them, and existing musculoskeletal assessment tools may lack the necessary sensitivity to detect subtle functional changes. Heterogeneity in musculoskeletal status means GT recipients may not protect from bleeds in all circumstances, and so there will therefore be a need for physiotherapists to reinvent how to assess PwH, and to develop more sensitive tools based on function and movement. These may include gait analysis or balance assessment, and new assessment tools with better clinimetric properties.[8] Considerations for GT should also take into account the risk of different intensity levels for physiotherapy sessions. As for physicians and nurses, physiotherapists will be involved in education, and will play a role in ongoing communication both within the MDT and with the PwH. The impact of GT for physiotherapists will drive the evolution of competencies and development of tailored care plans to complement pharmacological management. Physiotherapists must be aware of the past in haemophilia to positively influence the future.

In GT clinical trials, psychologists have been involved in checking each PwH's motivations to go through with the procedure, the degree of their compliance, and dedication to the process. They also assess a person's mental status, and whether their expectations of the new treatment fit reality. GT represents a significant psychological change. Since birth, the personality of each PwH has been built with and around their haemophilia. When we execute GT, we take the haemophilia out of their body, but not necessarily out of their personality, and this can cause an identity disconnect. Some GT recipients may still wish to identify as a PwH, others may choose to refer to themselves as 'ex-haemophiliac'—or simply just a person. In addition, some comorbidities will remain, such as pre-existing articular or musculoskeletal problems, and these may still deteriorate over time. Another consideration is that GT recipients may feel the loss of the haemophilia community, and miss their interactions with the HTC, and the psychologist will have a role in reassuring GT candidates that they can remain part of this community if they wish. Another important psychological issue to address is potential anxiety around medical complications. This may arise due to the common memory of previous novel treatments that caused mass-disability and death in earlier haemophilia generations. People on the GT journey must get psychological support before, during, and after starting the treatment. Psychosocial teams must be involved in all the stages as part of a coordinated MDT in the spoke HTCs.

In summary, we highlight the changing roles of HTCs in supporting GT for haemophilia. We support the EAHAD position that first-generation GT should be managed using a hub-and-spoke model,[1] and acknowledge that the key to success of the GT journey will be collaboration and communication both within and between centres.

ACKNOWLEDGEMENTS

This letter was drafted based on the content of a symposium shared at EAHAD 2021. Wolfgang Miesbach prepared the content regarding physicians, Sara Garcia Barcenilla prepared the content on nurses, Sébastien Lobet prepared the content on physiotherapy, and Gaby Golan prepared the content on psychologists. Editorial support was provided by Marie Farrow of Synthesis Editorial Ltd. The EAHAD symposium and the development of this letter was funded by BioMarin and organised by ELM Medical. BioMarin had no involvement in the planning or writing of the manuscript, which was developed by the authors alone in collaboration with ELM Medical and Synthesis Editorial Ltd.

CONFLICT OF INTEREST

Wolfgang Miesbach has received research support from Bayer, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Takeda/Shire; travel support from Bayer, BioMarin, Biotest, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Takeda/Shire, uniQure; been on a speaker bureau for Bayer, BioMarin, Biotest, CSL Behring, Chugai. LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Takeda/Shire; and has been involved in advisory boards for Bayer, BioMarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Takeda/Shire, uniQure. Sara Garcia Barcenilla is employed by IdiPAZ-Instituto de Investigación Biomédica Hospital

Universitario La Paz. She has received speaker fees from Bayer, Sobi, Pfizer, Takeda, NovoNordisk, Roche, Biomarin, Octapharma. Advisory/consultant: Bayer, Sobi, Pfizer, Takeda, NovoNordisk, Roche, Biomarin. Sébastien Lobet has received research support from Pfizer; he has received speaker fees from Bayer, Takeda, BioMarin, Pfizer, Novo-Nordisk, Roche, Sobi; and been involved in advisory boards for Takeda, BioMarin, Roche. Gaby Golan has nothing to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Wolfgang Miesbach[1]
Sara Garcia Barcenilla[2]
Gaby Golan[3]
Sébastien Lobet[4,5,6]

[1] *Goethe University Hospital, Frankfurt, Germany*
[2] *Grupo 14 de Coagulopatías y alteraciones de la hemostasia, Hospital La Paz Institute for Health Research – IdiPAZ (La Paz University Hospital – Universidad Autónoma de Madrid), Madrid, Spain*
[3] *Israel National Haemophilia Centre, Tel Aviv Medical School, Tel Aviv, Sheba Hospital, Israel*
[4] *Saint-Luc, Université catholique de Louvain (UCLouvain), Brussels, Belgium*
[5] *Université catholique de Louvain, Secteur des Sciences de la Santé, Neuromusculoskeletal Lab (NMSK), Institut de Recherche Expérimentale et Clinique, Brussels, Belgium*
[6] *Secteur de kinésithérapie, Cliniques universitaires Saint-Luc, Brussels, Belgium*

Correspondence
Wolfgang Miesbach, Goethe University Hospital, Frankfurt, Germany.
Email: Wolfgang.Miesbach@kgu.de

ORCID

Wolfgang Miesbach https://orcid.org/0000-0001-8286-5398
Sara Garcia Barcenilla https://orcid.org/0000-0002-8706-0668
Sébastien Lobet https://orcid.org/0000-0002-3829-6850

REFERENCES

1. EAHAD. Available at: http://eahad.org/wp-content/uploads/2020/05/Hub-and-Spoke.pdf. Accessed: July 2021.
2. Miesbach W, Klamroth R. The patient experience of gene therapy for hemophilia: qualitative interviews with trial patients. *Patient Prefer Adherence*. 2020; 14: 767-770.
3. Miesbach W, O'Mahony B, Key NS, Makris M. How to discuss gene therapy for haemophilia? A patient and physician perspective. *Haemophilia*. 2019; 25: 545-557.
4. Majowicz A, Nijmeijer B, Lampen MH, et al. Therapeutic hFIX activity achieved after single AAV5-hFIX treatment in Hemophilia B patients and NHPs with pre-existing anti-AAV5 NABs. *Mol Ther Methods Clin Dev*. 2019; 14: 27-36.
5. García-Barcenilla S et al. New subcutaneous therapies and clinical trials: a survey on patient perspectives. Presented at EAHAD 2019 12th Annual congress, Prague. 2019 Hospital Universitario La Paz-IdiPAZ, Madrid, Spain.
6. Evens H, Chuah MK, VandenDriessche T. Haemophilia gene therapy: from trailblazer to gamechanger. *Haemophilia*. 2018: 50-59.
7. Stephensen D, de Kleijn P, Matlary RED, et al. Scope of practice of haemophilia physiotherapists: a European survey. *Haemophilia*. 2019; 25(3): 514-520.
8. Lobet S, Detrembleur C, Massaad F, Hermans C. Three-dimensional gait analysis can shed new light on walking in patients with haemophilia. *Scientific World Journal*. 2013: 284358.