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Evolution of Haemophilia Integrated Care in the Era of Gene Therapy: Treatment Centre's Readiness in US and EU

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Introduction

Comprehensive, integrated care provided by a multi-disciplinary team of experts improves outcomes and is widely recommended for people with haemophilia (PWH) [1-6]. Although care models vary, the principles of management are consistent between countries. The likely approval of gene therapy for PWH in the next few years has the potential to alter the course of disease and drive an evolution in haemophilia care [7, 8]. A group of haemophilia experts including physicians, a haemophilia nurse, a physiotherapist and PWH met in September 2020 to discuss strategies for safely introducing gene therapy into clinical practice, and to identify its potential long-term effects on haemophilia care models in the USA and Europe. Experts agreed on four universal principles for the introduction of gene therapy (Table 1) and furthermore identified a range of topics that need to be discussed and resolved locally in order to implement these principles. Going forward, national/regional haemophilia networks should lead the debate on the implications of gene therapy for haemophilia treatment centres (HTCs) and develop workable solutions to the challenges and opportunities that gene therapy presents.

1. Haemophilia Integrated Care Infrastructure

HTC care models in the short- and long-term

The introduction of gene therapy to PWH is likely to have a major impact on haemophilia care models and networks. The principle that PWH should have equal access to gene therapy as soon as it becomes available presents a number of challenges to HTCs given relatively few have experience with this new technology. Short-term monitoring of gene therapy recipients is likely to be intensive and to begin with, highly coordinated integrated models (e.g. 'hub and spoke') may be required to oversee all aspects of care [9]. Haemophilia gene therapy consists of three main work streams; supervising (overseeing all aspects of care); infusion (storage, preparation, administration and disposal of gene therapy); and follow-up (post treatment monitoring). If centres are only able to complete 1 or any combination of two tasks, they would partner with another centre to complete the necessary work needed for gene therapy (Figure 1). Supervising centres would be expected to meet pre-defined criteria, and to follow well-defined processes to ensure that PWH are fully aware of the risks and benefits of gene therapy prior to dosing. HTCs with gene therapy clinical trial experience may have a short-term advantage in this regard. In some countries, specialist gene and cell therapy centres of excellence may administer gene therapy. Follow-up and data reporting should be conducted at centres with expertise in data collection and sharing, and systems should be standardised using resources such as the World Federation of Hemophilia Gene Therapy Registry (WFH GTR) [10-12]. Over time, gene therapy expertise and knowledge must be shared across haemophilia care networks to ensure that access to gene therapy is not limited by a lack of knowledge or capacity. This needs a coordinated approach by National/regional groups.

Changes to the coordinated care team

In the short-medium term, HTCs are likely to require additional resources to co-ordinate care and follow-up gene therapy recipients, in addition to their usual responsibilities. Physicians and nurses will be required to educate PWH about gene therapy, and will play key roles in developing standards for gene therapy eligibility and screening candidates. Additional investment in psychosocial support may be required to ensure that PWH and their families/care givers are fully informed about the risks and benefits of treatment and are appropriately supported after gene therapy dosing. New processes for ordering, storing, handling and reconstituting gene therapy products may lead to changes for pharmacists; and the need to

monitor the liver health of gene therapy recipients, particularly in the first months, may increase demands on hepatology. Physiotherapists will need to continue to monitor joint health in gene therapy recipients using physical assessment tools and (where possible) musculoskeletal ultrasonography. Physiotherapists will also be required to provide rehabilitative interventions and exercises for gene therapy recipients. The number of orthopedic interventions required may not significantly change in the short-to medium term; legacy joint problems will persist. Over the medium term, the incorporation of monitoring into standard operating procedures will enable the expansion of follow-up centres. Education and training of the entire team will be required to underpin these shifts, and careful thought given to resourcing requirements over time for HTCs offering gene therapy.

2. Treatment Guidelines and Protocols

Gene therapy treatment guidelines will influence local planning around individual selection, consent, and monitoring requirements. Local protocols should be established before the introduction of gene therapy, and should take into account the different stages of treatment (pre-treatment assessment and consent, dosing, and short- and long-term follow-up), scenario planning (day of infusion plans, management of adverse events and changes in liver function, and immunosuppression requirements), resource availability and geography, and payment/reimbursement plans. Recommendations should be feasible, acceptable to PWH, and should be led by the haemophilia community, including HTC experts, professional societies, and patient organisations.

Given the potential risks and uncertainties surrounding the long-term safety and efficacy of gene therapy, careful consideration should be given to the informed consent process. Genuinely shared decision making is required, based on open and honest dialogue between gene therapy experts, PWH and their families/carers. Responsibility for the development of protocols in this regard ultimately lies with the haemophilia community.

Life-long data collection requirements and the roles and responsibilities of HTCs should be agreed at a local level using published frameworks [10,11]. Where possible, the burden on gene therapy recipients should be minimised through gathering the minimum information required

for safe care and the advancement of scientific knowledge, and (for those who require less intensive follow-up) by collecting information via Telehealth, E-platforms or remote outreach programmes. Patient organisations will play a key role in reinforcing positive relationships between follow-up centers and gene therapy recipients, in updating center information and supporting the HTCs, individuals concerned and caregivers in ongoing education and follow-up. The development of a 'Memorandum of Understanding' or 'Patient Charter' that supports shared decision making is worthy of consideration; patient organisations could play a central role here.

3. Education, Collaboration, Communication

Currently, expertise in gene therapy is highly localised. To ensure equity of access and the long-term success of gene therapy, expertise will need to be disseminated across the haemophilia community. Numerous groups including the International Society on Thrombosis and Haemostasis (ISTH), World Federation of Hemophilia (WFH), American Thrombosis and Hemostasis Network (ATHN), European Association for Haemophilia and Allied Disorders (EAHAD) and European Haemophilia Consortium (EHC), provide valuable resources for the haemophilia community in terms of gene therapy education and Registry/data collection. However, greater efforts are needed to raise awareness of gene therapy, and to educate PWH and healthcare professionals about gene therapy techniques and procedures, potential risks and benefits, and requirements for long-term follow-up. Patient organisations will play a key role in this process and its success.

A major challenge for gene therapy is that PWH tend to develop high levels of trust in their treating healthcare provider/HTCs and are rarely transferred between HTCs outside of clinical trials. Consequently, PWH may not wish to transfer to a new HTC in order to receive gene therapy unless this coincides with essential changes in care, such as a geographical relocation or the transition to an adult supervising centre for someone cared for within a paediatric setting. A new operational model of collaborative care is required to overcome this challenge. This will require a shift in attitude and working practices that could be encouraged by the provision of freely available information on gene therapy availability and HTC expertise.

Effective communication will be essential to ensure that PWH and their families/carers are central to decision making and fully understand their follow-up obligations. This will involve open and objective discussions about what is important to the individual in terms of treatment needs, measures of success, and potential risks and benefits [8]. Information sharing needs to be transparent and prompt. The development of tools that reinforce gene therapy recipient's commitment to follow-up should be considered. All PWH should be aware of standard procedures for monitoring and reporting well-defined treatment outcomes at pre-determined time points, and strategies for managing adverse events. Care providers at referring centres and gene therapy HTCs should regularly review progress, and gene therapy recipients should know who to contact should they have any concerns or questions. Continuous education and strategies that ensure the rapid dissemination of data across HTCs worldwide will be required as experience grows.

4. Reimbursement and funding

Competition between HTCs due to current differences in funding flows may have a detrimental effect on HTC viability, HTC collaboration and, consequently, the long-term success of gene therapy. For example, US HTCs currently rely on 340B Pharmacy support (a system that allows HTCs to purchase pharmaceutical products at discounted rates and sell them to their patients at a profit) to fund vital services that are otherwise non-reimbursable [13]. Gene therapy could therefore have a profound impact on HTC viability in the US unless appropriate funding/reimbursement models for delivery of gene therapy care (not just dosing) are developed. Solutions for this will need to be developed at a National/Regional level by payers, with input from the haemophilia community, and planning should start ahead of gene therapy availability.

Summary

Multi-disciplinary integrated HTCs have demonstrated their value in improving outcomes, quality of life, and education for PWH [1, 2, 6]. Studies suggest this may be especially important for individuals with a higher disease burden and/or those with higher resource requirements

[3]. Significant work will be needed to prepare HTCs for the safe introduction of gene therapy to ensure that gene therapy recipients are carefully treated and monitored. Support from the haemophilia community, payers and industry partners will be essential to ensure that HTCs have the resources they need to meet these challenges.

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Links to: International Society on Thrombosis and Haemostasis (ISTH); World Federation of Hemophilia (WFH); American Thrombosis and Hemostasis Network (ATHN); European Association for Haemophilia; Allied Disorders (EAHAD) and European Haemophilia Consortium (EHC)

Conflicts of Interest:

WM has served as a paid consultant of Alnylam, Bayer, Biomarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Takeda and uniQure

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Table 1: Four universal principles for the introduction of gene therapy to people with haemophilia

▪ The PWH should be at the centre of decision making
▪ All PWH should have an equal opportunity to access gene therapy
▪ The safe introduction of commercial gene therapy with lifelong follow-up is paramount to ensuring long-term success

- The integrated comprehensive care model currently employed for the treatment of haemophilia improves outcomes and is best placed to support the introduction and long-term follow-up of gene therapy

Fig 1: Potential Division of Responsibilities Among One or More Centres

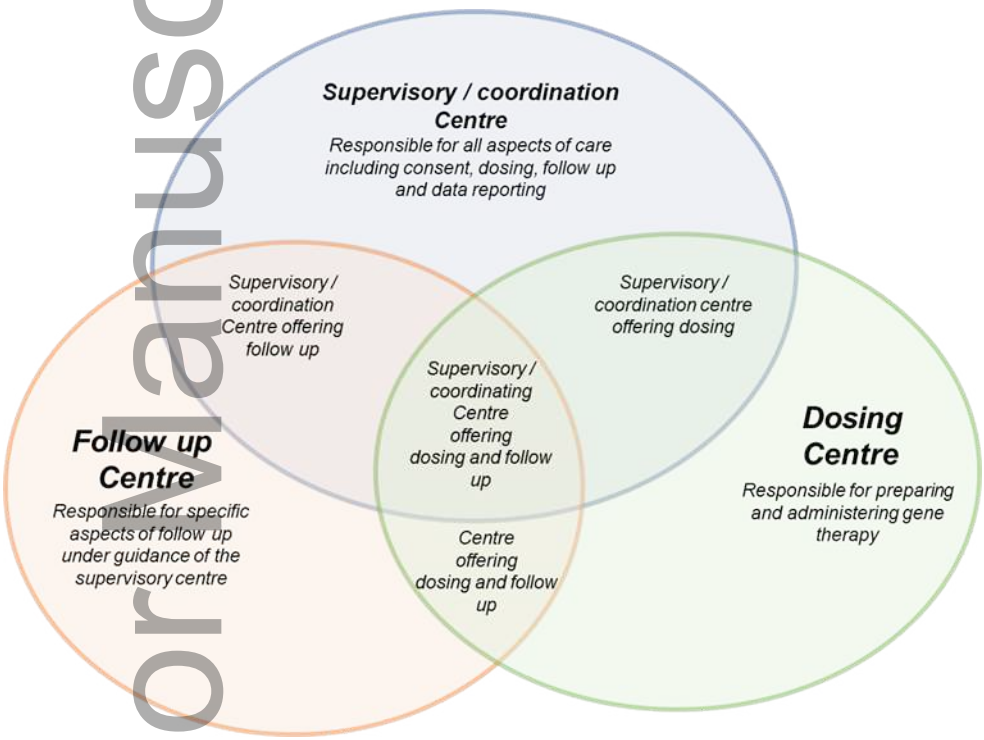

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Figure 1. Areas of responsibility. A centre may serve one or more of these roles