








Delivery of AAV-based gene therapy through haemophilia centres—A need for re-evaluation of infrastructure and comprehensive care: A Joint publication of EAHAD and EHC

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Abstract

Introduction: Adeno-associated virus (AAV)-based gene therapy for haemophilia presents a challenge to the existing structure of haemophilia centres and requires a rethink of current collaboration and information exchange with the aim of ensuring a system that is fit-for-purpose for advanced therapies to maximise benefits and minimise risks. In Europe, a certification process based on the number of patients and facilities is offered to the haemophilia centres by European Haemophilia Network (EUHANET).

Aim and methods: This joint European Association for Haemophilia and Allied Disorders (EAHAD) and European Haemophilia Consortium (EHC) publication describes criteria for centres participating in gene therapy care that require a reassessment of the infrastructure of comprehensive care and provides an outlook on how these criteria can be implemented in the future work of haemophilia centres.

Results: The core definition of a haemophilia treatment centre remains, but additional roles could be implemented. A modifiable 'hub-and-spoke' model addresses all aspects associated with gene therapy, including preparation and administration of the gene therapy product, determination of coagulation and immunological parameters, joint

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score and function, and liver health. This will also include the strategy on how to follow-up patients for a long-term safety and efficacy surveillance.

Conclusion: We propose a modifiable, networked 'hub and spoke' model with a long term safety and efficacy surveillance system. This approach will be progressively developed with the goal of making haemophilia centres better qualified to deliver gene therapy and to make gene therapy accessible to all persons with haemophilia, irrespective of their country or centre of origin.

KEYWORDS

gene therapy, haemophilia care, haemophilia treatment, treatment centres

1 | INTRODUCTION

The treatment of haemophilia and adherence to prophylactic therapy has been significantly improved by the introduction of long-acting factor concentrates and non-factor therapy based on innovative technologies.¹ Additionally, haemophilia care, including the availability of factor concentrates and medical expertise, patient information and organisation have made considerable progress in recent decades. According to the third edition of the World Federation of Haemophilia (WFH) guideline, regular prophylaxis should start at a young age until an alternative long-term therapy such as gene therapy becomes available.² In line with these improvements, prophylaxis is now recommended for all patients, aiming for trough levels of at least 3–5% when using extended half-life Factor VIII (FVIII) and IX (FIX) concentrates.¹

The complex treatment of haemophilia has been managed by specialised, interdisciplinary European Haemophilia Comprehensive Care Centres (EHCCC's) and European Haemophilia Treatment Centres (EHTC's) that offer a wide range of clinical and laboratory services as well as the supply of factor concentrates for home treatment.³

Haemophilia treatment centres (HTC's) have been established to ensure the multidisciplinary care model with access to clinical specialties, emergency departments and appropriate laboratory facilities. Diagnostic and treatment tools were optimized to prevent bleeding and treat haemophilia-related comorbidities.

The European Haemophilia Network (EUHANET) project identified 409 haemophilia centres in Europe.⁴ It established a certification process based on the number of patients and facilities offered by the haemophilia centres. Centres are able to apply to be comprehensive care centres or haemophilia treatment centres.

The arrival of advanced therapies and particularly gene therapy requires further thought on appropriate ways to organize European haemophilia treatment centres. We propose a modifiable, networked 'hub and spoke' model with a long-term safety and efficacy surveillance system.

2 | GENE THERAPY AS A CHALLENGE FOR HAEMOPHILIA CENTRES

Gene therapy offers the promise for haemophilia patients to receive a one-time treatment, achieving potentially clinically meaningful fac-

tor levels that could last for years or decades, enabling independence from frequent and repeated administration of a prophylaxis agent. Some adeno-associated virus (AAV) vector-mediated gene transfer in haemophilia A and B are already in phase III trials.⁵ It is expected that the first FVIII and FIX gene therapy products will be approved in 2022, becoming available soon thereafter for patients with haemophilia in Europe, Middle East and the United States.

Although gene therapy strategies have been in development for more than 20 years, gene therapy for haemophilia is still a new and experimental method, with very few patients treated so far. Some adverse events are known from the studies published so far, remaining uncertainties and potential unknowns are widely discussed: short-term or mid-term safety issues include allergic reactions and liver enzyme elevations, which require prompt management. Patients and their caregivers have to deal with some uncertainties that are not encountered from current, conventional prophylaxis treatments.⁶ The response rate and persistence of expression may vary and, thus far, cannot be reliably predicted.⁷ For some patients who experience a loss of factor expression with re-emergent spontaneous bleeding, re-engagement with conventional comprehensive care will be necessary.⁸

The level of factor expression is considered the appropriate primary endpoint in gene therapy studies on haemophilia.⁹ The laboratory equipment of haemophilia centres includes a well-established, validated set of coagulation factor tests, which are able to quantify the effect of different treatments, assessing the efficacy and potential complications (e.g., inhibitors) of a given therapeutic agent. Measurement of factor levels in gene therapy, however, may require specific factor assay selection on account of there being discrepancy between the one-stage and chromogenic assay, with the one-stage assay being 1.6 times greater than the chromogenic assay in both HA and HB gene therapy.¹⁰ In addition, regular laboratory values in blood such as blood count, haemoglobin and clinical chemistry including kidney and liver markers need to be measured. Liver enzymes are particularly important in gene therapy, because liver-specific gene therapies can cause liver toxicity, and patients need to be evaluated carefully with expert hepatologists and immunologists.

The approach of gene therapy for haemophilia is to achieve better clinical outcomes and a better quality of life than is possible with currently available haemophilia products. For this, there should be a

global effort to make this therapy available to interested patients so that equal access can be guaranteed.⁶

With the introduction of gene therapy, the requirements for EHCCC's and EHTC's will change, representing a fundamental paradigm shift in the treatment of haemophilia, with many potential consequences for haemophilia centres. Among other things, long-term follow-up in clinical trials and registries is required and a coordinated approach by all stakeholders is necessary to ensure safe and effective application, as well as to initiate immediate coordinated action in case of unexpected safety problems, with the aim of offering every patient an optimal chance of success and provide better information for decision-making by both clinician and patient.^{11,12}

An additional new task would be to follow and monitor the selection criteria for gene therapy in patients. Up to now, a significant number of patients cannot be treated with gene therapy, as in many cases exclusion criteria for gene therapy exist, for example, the presence of pre-existing antibodies against AAV, age younger than 18 years or comorbidities.⁵ In clinical trials, gene therapy also requires a non-routine measurement of cellular and humoral immunity as well as the determination of the release of vector particles through body fluids (vector shedding). One of the selection criteria for the majority of gene therapy platforms is the absence of already existing antibodies to AAV, which may limit the possibility of liver cell transduction and consequent factor expression. After successful transduction, a T-cell dependent response has been described that leads to transaminitis and liver cell damage.⁵ None of these tests are standardized or utilise commonly used reagents, which makes inter- and intra-laboratory comparison of antibody levels or T-cell titres difficult. However, it is not clear what tests need to be transposed from the clinical trials into service delivery and what can be dropped. These criteria may change over time based on evidence from subsequent studies that include these patient groups. Further studies are planned in patients with coagulation factor inhibitors and in children and adolescents.

Very few centres will currently have access to assays for measuring specific B- and T-cell immune responses, and strategies should be developed for collaboration with experienced laboratories or industry.

In addition to laboratory issues, time, resources and clinical capacity to deliver gene therapy, expertise to monitor and manage unexpected adverse events or to determine the dosage or duration of prophylactic and concurrent immune suppressive treatment when necessary to overcome liver toxicity, is required.¹³ Protocols on different strategies for immunosuppression as performed in the different studies should be provided.

More personalised discussions about patient expectations would be appropriate, anticipating the likely changes in the circumstances affecting patients' lifestyle after discontinuing regular prophylactic treatment. Psychological support needs to be provided in a robust and consistent manner, as early as the decision-making stage on whether or not to choose gene therapy, considering its possible short and long-term safety problems or other unknown factors, for example, the durability of gene expression.⁹

Lack of knowledge and familiarity with gene therapy has also been expressed by European pharmacists, including concerns about phar-

TABLE 1 Challenges of gene therapy for haemophilia centres

- Patient informed consent and eligibility tests
- Administration of a gene therapy construct and managing infusion related reactions
- Monitoring variability of factor expression and deciding when to stop prophylactic treatment
- Close cooperation with hepatologists and immunologists
- Monitoring of short-, medium- and long-term adverse events
- Retaining patient engagement for follow up
- Long-term follow-up by an accurate surveillance system
- Direct and indirect costs reimbursement for administration of gene therapy and follow-ups

macokinetic and pharmacodynamic interactions.¹⁴ In addition, conditions for appropriate equipment may be lacking and must be prepared accordingly, such as facilities for storage, handling and reconstitution of gene therapies.¹⁵ In some countries not only healthcare legislation applies but also environmental legislation. This is, for example, the case in Holland where one needs an environmental permit and all academic hospitals need to have a biosafety officer when dealing with genetically modified organisms.

The knowledge gap in gene therapy has led to the development and implementation of training programmes such as 'Gene therapy for haemophilia: An ISTH training initiative' that will be able to guide institutional preparation when approved gene therapy products become available. Additional efforts in post-marketing surveillance, patient registration and data collection have been initiated by WFH in collaboration with the International Society on Thrombosis and Haemostasis (ISTH), the European Association for Haemophilia and Allied Disorders (EAHAD), the European Haemophilia Consortium (EHC), the National Haemophilia Foundation (NHF) and other organizations.^{16,17}

Gene therapy for haemophilia presents a challenge to the existing structure of haemophilia centres and requires an enhanced modality of collaboration and information sharing with the aim of maximising benefits and minimising risks. Table 1 describes the challenges of gene therapy for haemophilia that can only be addressed through a collaborative effort among haemophilia centres and requires a re-evaluation of infrastructure and comprehensive care.

3 | THE HUB AND SPOKE MODEL OF DELIVERING GENE THERAPY IN HAEMOPHILIA CENTRES

The proposed 'hub and spoke' model aims to coordinate a complete package of care of gene therapy delivery, ensuring sufficient time and expertise for patient counselling and informed consent, with clear demarcation of responsibility for subsequent dosing,

micromanagement (close surveillance) of the immediate post infusion time period and then offering patient centric long term follow-up and surveillance. We recognise that this model will need to be modifiable for different countries and even between regions of the same country.

There are broadly 2 scenarios:

- 1- The 'Hub' is a HTC experienced in both comprehensive care and gene therapy (GT) and the 'Spoke' is another HTC with no or minimal GT experience, which will be the home centre for the patient. The Hub in this scenario will take the lead in all aspects of GT delivery pre infusion and post infusion. Although the patient may be managed locally (visits, routine bloods, MDT review), decisions relating to GT will remain a collaborative discussion between the Hub and Spoke staff to ensure optimum patient outcomes.
- 2- In this scenario the 'hub' is a dosing centre (GT delivery experienced) and the 'Spoke' is a management centre (also GT experienced). To offer a full range of gene therapy platforms, patients may need to go to other sites for infusion, as it is possible that not all centres will have all platforms open, but return to their 'home' centre for subsequent management.

In either scenarios, it is important to guarantee that hub and spoke centres follow all patients regularly, particularly in the first year with well-defined and structured protocols.

Clinical gene therapy studies have been conducted in specialized HTC's, with HTC's often benefiting from their research pharmacies, clinical research centres, dedicated research nurses and coordinators. In the recently published joint statement of EAHAD and EHC, a gene therapy hub and spoke model was proposed to ensure safe introduction, use, monitoring and optimal learning capacity for all eligible patients.¹⁸

The core, traditional definition of an HTC may remain, but it may be useful to add additional tasks to be implemented before and/or after the administration of gene therapy. A hub and spoke model would deal with all aspects inherent to gene therapy, including informed consent, preparation and administration of the gene therapy product, determination of coagulation and immunological parameters, joint score and joint function, surgery and liver health, among others. In light of experience with gene therapy studies, several criteria have emerged that a gene therapy treatment centre should fulfil. These criteria could only be met by a small number of HTCs, which could serve as dosing centres (hubs) for patients from other HTCs (spokes) with whom close cooperation could be established (Table 2).

In this proposed model, the tasks would be divided according to the experience and equipment of the partner centres (Table 3). Gene therapy is exclusively prescribed and administered by expert haemophilia comprehensive care centres (as the hubs) and longitudinally monitored by haemophilia treatment centres in close communication with the primary expert hub (as spokes linking into that hub) depending on pre-existing expertise in each centre (see above scenarios 1 and 2).

In case that the patient was referred for dosing by another HTC, tests for the gene therapy program and existing antibodies against AAV need to be planned. Confirmation of informed consent should be car-

TABLE 2 Criteria for definition of gene therapy delivering centre (hub centre)

- Experience obtained in previous gene therapy trials (or specialists who can provide timely expertise in gene therapy) or available mentorship program
- Ability to order, store, prepare and administrate the gene therapy product
- Provision of informed consent
- Ability to perform diagnostic tests for the gene therapy program and follow-up of patients (e.g., modified chromogenic test)
- Close cooperation with other HTC's (interaction between HUB and SPOKE)
- Knowledge in timely diagnosis and management of adverse events in gene therapy
- Close cooperation with hepatologists and immunologists
- Protocols on different strategies for immunosuppression as performed in the different studies
- Longitudinal data collection and evaluation in gene therapy; for example, national and/or international registries

ried out to ensure all patients knowledge is up to date and reduce the risk of 'buyer's remorse' (regretting the decision to proceed with an irreversible process).

After the referred patient has been dosed, the 'home' HTC and spoke centre would remain responsible for patient follow-up, which should be done in close cooperation with the dosing centre, for example, in case of adverse events and the need for immunosuppressive treatment and any eventual need for inpatient care.

Particularly in the early post-dosing period, further regular follow-up by the hub centre can be performed, which in the long-term could be expanded to occasional reviews to detect unexpected long-term safety issues.

Management of bleeding events would remain the responsibility of the spoke centre. While the regular follow-ups are more intense in the first year, long-term follow-up, reporting and monitoring of adverse events and inclusion in a gene therapy database will need to be determined within that specific network of centres delivering the GT.

4 | EDUCATION OF THE MULTIDISCIPLINARY TEAM

In general, not only general tasks for HTCs change, but also the responsibilities of their multidisciplinary teams. The haemophilia nurse of the involved centres is likely to remain the patient's primary contact person to ensure coordination between the various centres, specialties and laboratories. Psychological support is likely to be required for several years after gene therapy and could become even more important as patients might experience chronic, or acute uncertainties and fears

TABLE 3 Responsibilities of the hub and spoke centres

	Hub	Spoke
Counselling about treatment options and discussing expectations	Renew this discussion before dosing	2–3 times during the pre-dosing process
Patient selection	Review of the eligibility criteria	<u>Patient recruitment or retention</u> <ul style="list-style-type: none"> Monitoring the eligibility criteria Identifying possible candidates
Laboratory monitoring and performance of diagnostic tests for the gene therapy program	<u>Required test before treatment:</u> -existing AAV-antibodies	<u>Required test before treatment:</u> Pre-existing AAV-antibodies <u>Required after treatment:</u> <ul style="list-style-type: none"> Determination of possible immunological markers Coagulation factor levels
Education and training	Training of health professionals from other HTC and management advice (e.g., corticosteroid treatment)	Multidisciplinary team to be trained
Informed Consent	Review before dosing	Education and regularly follow-up of patients and physicians
Preparation of the gene therapy product, dosing	Storage of materials for preparation and administration	
Follow-up		
Short-term	<ul style="list-style-type: none"> Counselling and collaboration Further regular follow-up can be performed Protocols on different strategies for immunosuppression as performed in the different studies 	<ul style="list-style-type: none"> Regular follow-up (weekly to monthly) at least in year 1), Initiation of immunosuppressive treatment
Long-Term (from year 2)	<ul style="list-style-type: none"> Counselling about long-term risks Follow-up can expand to occasional reviews 	<ul style="list-style-type: none"> Regular follow-up (every 3 until 6 months) Liver health review
Data collection	National and international data collection ¹⁷	National and international data collection ¹⁷
MDT Team	<ul style="list-style-type: none"> Counselling and collaboration 	<ul style="list-style-type: none"> Ongoing support of bleeding episodes or management of any side effect Ensure information sharing with Hub If possible:

Abbreviations: HTC, haemophilia treatment centre; AAV, adeno associated virus; MDT, multidisciplinary team.

after gene therapy, either platform specific or more generic, depending on future events in longer term follow up of the global cohorts of gene therapy recipients.⁶

The members of the HTC multidisciplinary team should be trained and provided with up-to-date information on all relevant aspects of gene therapy with the aim that each member of the HTC is informed about gene therapy, and patients receive consistent information. Gene therapy training should also be included in the undergraduate and post-graduate curricula.

Within the HTC multidisciplinary team, the role of the hepatologist needs to be defined in terms of their importance and clinical contribution in the recognition and management of short-term and possible long-term adverse events of gene therapy. It may be prudent to involve

a hepatology specialist in the pre-dosing period to discuss personalised liver health and potential risks with a gene therapy candidate.

The issue of reimbursement for gene therapy refers to the overall funding for centres providing gene therapy, and goes beyond the costs of gene therapy itself. Sustainable funding solutions should be developed on a national basis including the costs for the hub and spoke centres' infrastructure and staff costs.

A close collaboration with pharmaceutical/life science industry partners is required, taking into account both their past experience and current gene therapy activity, as well as with scientific organisations, patient organisations, payers/commissioners and regulatory authorities on how to ensure long term observation and evaluation of gene therapy recipients.

5 | CONCLUSION

Gene therapy offers the possibility to transform patients' lives by enabling a long-lasting period of high levels for factor expression, possibly into the normal range, after a single therapeutic infusion. Although many early recipients may have legacy haemophilic arthropathic changes persisting post GT, such sustained levels of factor expression is likely to provide sustained freedom from spontaneous bleeds and normalise risk of traumatic bleeds to that of non-haemophilic peers. Uncoupling the individual GT recipient from the requirement for regular administration of a haemostatic therapy to maintain their protection is likely, in time, to harness a much broader personal 'freedom' to pursue activities and opportunities, both recreational or occupational, whether close to home or much further a field, possibly to parts of their country (or the globe) that they would have never previously considered travelling to through necessity of risk assessment for acute care.

Given the complexity and potential complications of gene therapy administration, it is the responsibility of health professionals to ensure the prescription, administration and monitoring of gene therapies. This proposed 'hub and spoke' model according to the joint statement of the EAHAD and the EHC offers patients the opportunity to receive gene therapy independent of their location or state of knowledge or experience of their local haemophilia centres and obtain the best outcome available in the short and longer term. However, raising awareness and education for both patients and health care personnel (physicians, nurses, physiotherapists, psychologists, lab team) in the wider network of HTC is crucial as most follow-up will be done through the local centres.

Currently, a minority of patients will be eligible for gene therapy but with time, inclusion criteria will change and more gene therapy products will become available. With more experience it is likely that the knowledge and also the outlined responsibilities may change, and the criteria for a hub and a spoke model could be adjusted accordingly.

The strength of a hub and spoke model for managing gene therapy is to enable standardised gene therapy treatment of haemophilia patients, regardless of the centre or even country in which the patients are located. In addition, quality criteria could be established and approved to ensure a robust informed decision, with the maximum benefit of gene therapy and the least possible side effects, as well as a strong working team comprised of pharmacists, nurses, hepatologists, psychologists, physiotherapists, biomedical scientists and haematologists.

This model is expected to be dynamic and would be adaptable based on gene therapy efficacy and safety data to be better prepare for the challenges of delivering this therapy type once they are approved.

Although this manuscript only addresses the challenges of AAV-based gene therapy, it may pave the way for some more specific future requirements for non-AAV-based approaches and ex vivo gene therapies.

In summary, gene therapy is becoming an increasingly important therapeutic option for patients with haemophilia. This therapeutic modality requires additional interaction with other specialties including hepatologists, and in addition it is important that clinical

experience about nuances of gene therapy is gained and shared. Further, long-term surveillance is absolutely critical for demonstrating the long-term safety not just for GT recipients with haemophilia but also cross referencing with experience and outcomes for patients with other monogenic disorders undergoing gene therapy.

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CONFLICTS OF INTEREST

WM: Bayer, Biomarin, Biotest, CSL Behring, Chugai, Freeline, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Takeda/Shire, uniQure. VJY: Bayer, Biomarin, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Takeda/Shire. DPH: Bayer, Biomarin, Biotest, CSL Behring, Grifols, NovoNordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, Spark, Takeda, UniQure. RK: Research Funding and Consultancy: Bayer, Biomarin, Biotest, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche/Chugai, Sanofi, SOBI, Takeda/Shire, uniQure. MM participated in advisory boards run by Freeline, Spark Therapeutics and NovoNordisk. MC: Research support: Bayer, CSL Behring, Roche, Sanquin Blood Supply, UniQure; Consultancy or lecturing fees: Bayer, CSL Behring, Medcon International, MEDtalks, NovoNordisk, Pfizer, Sobi. PC: advisory boards for Bayer, Boehringer Ingelheim, CSL Behring, Chugai, Freeline, NovoNordisk, Pfizer, Roche, Sanofi, Spark, Sobi and Takeda; and has received research funding from Bayer, CSL Behring, Freeline, Novo Nordisk, Pfizer, SOBI and Takeda. FP: speaker at educational symposia organized by Roche, Sanofi, Sobi, Takeda. Member of Advisory Board of Roche, Sanofi, Sobi, Takeda.

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