











RECOMMENDATIONS AND GUIDELINES

Core data set on safety, efficacy, and durability of hemophilia gene therapy for a global registry: Communication from the SSC of the ISTH

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Abstract

Background: Gene therapy for people with hemophilia (PWH) will soon become available outside current clinical trials. The World Federation of Hemophilia (WFH), in collaboration with International Society of Thrombosis and Hemostasis Scientific and Standardization Committee (ISTH SSC), the European Haemophilia Consortium (EHC), the US National Hemophilia Foundation (NHF), the American Thrombosis and Hemostasis Network (ATHN), industry gene therapy development partners and Regulatory liaisons have developed the Gene Therapy Registry (GTR), designed to collect long-term data on all PWH who receive hemophilia gene therapy.

Objective: The objectives of the GTR are to record the long-term safety and efficacy data post gene therapy infusion and to assess the changes in quality of life and burden of disease post-gene-therapy infusion.

Methods: The GTR is a prospective, observational, and longitudinal registry developed under the guidance of a multi-stakeholder GTR Steering Committee (GTR SC), composed of health care professionals, patient advocates, industry representatives, and regulatory agency liaisons. All PWH who receive gene therapy by clinical trial or commercial product will be invited to enrol in the registry through their hemophilia treatment centers (HTCs). The registry aims to recruit 100% of eligible post gene therapy PWH globally. Through an iterative process, and following the guidance of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), the GTR SC has developed a core set of data to be collected on all patients post gene therapy.

Results: The core data set includes demographic information, vector infusion details, safety, efficacy, quality of life and burden of disease.

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Conclusions: The GTR is a global effort to ensure that long term safety and efficacy outcomes are recorded and analysed and rare adverse events, in a small patient population, are identified. Many unknowns on the long-term safety and efficacy of gene therapy for hemophilia may also be addressed.

KEYWORDS

core data, gene therapy, hemophilia, registry, safety

1 | BACKGROUND AND STRATEGY

The first gene therapy product for people with hemophilia (PWH) is expected to receive regulatory approval in 2020, with several additional approvals close on the horizon. Current data on these emerging technologies suggest a potential “functional cure,” with bleeding essentially eliminated in the majority of treated hemophilia patients.¹⁻³ Although the potential for these transformative gene therapies is great, emerging technologies by definition have unknown safety and efficacy risks.⁴ Most of these gene therapies will be evaluated and approved based on small cohort trial enrollment with limited duration follow-up. This imposes a heavy reliance on the postmarketing experience to gather critical evidence of safety and durability.⁵

Current late-phase gene therapy trials for hemophilia A and B are using an adeno-associated viral (AAV) vector for targeted in vivo hepatocyte expression.¹⁻³ Naturally occurring AAV is a member of the *Parvoviridae* family and is generally considered nonpathogenic.⁶ Although clinical trial data provide reassurance of short-term safety and efficacy of AAV-mediated gene therapy, we are entering this new treatment era with remaining questions of short- and long-term safety. Safety issues identified to date include hepatic inflammation, due, at least in part, to an AAV capsid-mediated immune response, and a febrile reaction that may occur usually within 48 hours of vector infusion.^{4,7,8} The asymptomatic increase in liver transaminases is generally vector dose-dependent and usually, but not always, responsive to a course of steroid therapy. The optimal approach to immunosuppression in this setting has yet to be defined and prophylactic regimens are being evaluated.

Safety risks include currently unknown risks, but there are also known issues that will need to be monitored such as risks of long-term hepatic toxicity and genotoxicity, particularly in patients with prior viral infections, and the risk of insertional mutagenesis.⁴ Although AAV is predominantly a nonintegrating virus, integration events demonstrated in large animal and humans, post-AAV gene transfers occur at an estimated frequency of approximately 0.1% per transduced cell.^{4,7,9} Hepatocellular carcinoma was seen in one liver-directed recombinant AAV preclinical murine study¹⁰; a larger study found that hepatocellular carcinoma risk depended upon vector dose, promoter, enhancer, and the degree of hepatic cell division during vector administration.¹¹ A 10-year follow-up of AAV-mediated factor VIII (FVIII) expression in dogs detected integration events and evidence of clonal expansion in liver tissue, but there was no evidence of hepatocyte damage or tumorigenesis.¹² The only available study of human liver tissue postintravascular

TABLE 1 Summary of key areas of core data collection for gene therapy^a

Demographics

Medical/clinical history

Gene therapy infusion details

Safety data

Adverse events of interest

FVIII/FIX inhibitors

Thromboembolic events

Autoimmune disorders

Malignancies

Liver function

Death

Efficacy data

Bleeding events

Factor activity levels

Use of hemostatic treatment

Patient reported outcome measures

Quality of life

Burden of disease

Mortality

^aSee Table S1 for full core data set.

AAV delivery demonstrated evidence of random integration events without evidence of genotoxicity or clonal expansion.⁹

At this point, it is unknown how long a gene therapy effect will persist. Factor IX activity has persisted at stable levels of ~5% in the high-dose cohort of the St. Jude/UCL phase 1/2 trial with more than 9 years of follow-up.³ Whether similar long-term stable expression will be seen in trials currently achieving higher FIX levels through the use of the FIX Padua construct has yet to be shown, although initial results are promising.^{3,8} In patients with 3 years of follow-up after F8 gene therapy (AAV5-hFVIII-SQ), some of whom initially had levels well into or above the normal range, the median chromogenic FVIII activity was 20% in the highest dose cohort (6×10^{13} vg/kg).¹³ Whether levels will stabilize or gradually fall is unknown. In terms of efficacy measured by bleeding events, overall, most trials have shown a remarkable decrease in bleeding and factor usage and improved quality of life.^{1-3,7,8,13} However, only longer term data will answer the questions around efficacy and durability and identify differences should they exist by vector or transgene used.

Ultimately, the accumulation of patient exposure captured in long-term registries is the most likely means of revealing unexpected events associated with this new technology. Detecting low incident or delayed safety events, particularly in small treatment cohorts of a rare disease, necessitates that each PWH who receives gene therapy be followed over the long term, preferably their lifetime, in a registry that has as its goal inclusion of all treated patients. Additional approaches to gene therapy for hemophilia are under study in pre-clinical and early clinical models including use of gene-editing, lentiviral vector, and cellular therapies.^{3,8,14} These will carry common and unique risks and benefits compared with AAV-mediated gene therapy and postmarketing surveillance will need to be adaptable to new safety signals and new endpoints as the field evolves.¹⁵ Additionally, registration trials are being performed in a healthy subset of patients, and restrict use of comedications, thereby reducing the likelihood of detecting disease–drug and drug–drug interactions.¹⁶

A collaborative global strategy is required to ensure a large enough patient pool to allow robust evaluation and detection of low incident events that may otherwise go undetected. If events are captured in disparate registries or databases, we will regrettably not benefit from the power of combined data. As the field continues to make progress, a growing set of long-term safety and efficacy data will ultimately define the future of gene therapy in hemophilia. For a long-lasting, potentially life-long, therapy, we need data collection over the lifespan of treated patients, longer than the mandated follow up by the US Food and Drug Administration of 5 years.¹⁷

The World Federation of Hemophilia (WFH), working with the International Society on Thrombosis and Hemostasis (ISTH), along with the European Haemophilia Consortium, the US National Hemophilia Foundation, the American Thrombosis and Hemostasis Network (ATHN), industry developer partners, and regulatory liaisons, is developing a global gene therapy registry. This registry will use a core data set, with input from a multistakeholder steering committee. Guidance from the US Food and Drug Administration and European Medicines Agency has informed the registry and specific data elements.¹⁷⁻¹⁹

Areas of focus of the core data set are shown in Table 1 and the full data set in Table S1. The aim of the gene therapy registry project is to provide a core data set integrated into a robust, scientifically valid registry, which is available to all physicians treating PWH who receive gene therapy. A patient mobile application will integrate patient reported outcomes directly into the registry. The data stemming from this registry will provide for robust surveillance of safety and efficacy of gene therapy.

2 | IMPLEMENTATION OF THE WFH GENE THERAPY REGISTRY

The WFH gene therapy registry is a prospective, observational, and longitudinal registry. All PWH who receive gene therapy, via clinical trial or postregulatory approval, will be encouraged to participate, with an aim to enroll nearly 100% of eligible PWH globally. Patients who do not provide informed consent to participate will be asked to give the reason to account for potential selection bias in enrollment. Clinical trial

participants will be enrolled following the closure of their trials, and postapproval PWH will be enrolled at the time of vector infusion.

Widespread successful implementation of this global registry is critical to its success. Outreach activities to educate hemophilia providers and PWH about the importance of surveillance are beginning. The WFH will collaborate with individual hemophilia treatment centers (HTCs) and existing gene therapy registries to leverage established data repositories. As an example, in the United States, ATHN is developing a gene therapy study (ATHN-14: Hemophilia Gene Therapy Outcomes Study) and working with the WFH to ensure harmonized data collection between the two registries. Where collaboration with an existing gene therapy registry is not currently available, HTCs participating in gene therapy trials, HTCs with plans to become an infusion center postregistration as well as HTCs that will follow their patients who have received gene therapy at an infusion center, are being contacted to plan for implementation. Financial reimbursement for provider and patient effort and expenses is planned. Integrating the collection of data into the clinical practice of physicians and the daily lives of PWH, requires a harmonious and uniform data collection methodology, that will be accepted and used by all stakeholders.

Data from this global gene therapy registry will be critical to answer questions regarding safety and efficacy of gene therapy in hemophilia. Given that hemophilia is a rare disease, it is imperative that we have a global approach to data collection to detect low incidence events that may affect the lives of PWH who choose to undergo gene therapy. The registry will also be able to measure and compare the impact of gene therapy on the lives of PWH around the world. Success of this ambitious initiative needs the support of all stakeholders. Only through cohesive efforts by all treating physicians, PWH, regulatory agencies and manufacturers worldwide, will we ensure that gene therapy is safe and efficacious for our patients now, and in the future.

CONFLICT OF INTEREST

All authors have declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

Donna Coffin provided the first draft of the registry content. All authors contributed in the critical content evaluation, editing, analysis, interpretation, and review through a series of online meetings. Barbara Konkle, Glen Pierce, and Donna Coffin drafted the first manuscript, which was critically evaluated, edited, and approved by all authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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