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

Konkle BA, Pierce GF, Coffin D, Naccache M, Clark C, George LA, Iorio A, O'Mahony B, Pipe S, Skinner MW, Watson C, Peyvandi F, Mahlangu JN, for the ISTH subcommittee on Factor VIII, Factor IX and rare bleeding disorders.

Key words: Gene therapy, registry, hemophilia, core data, safety

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 [1,2,3]. 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 post-marketing experience to gather critical evidence of safety and durability [5].

Current late phase gene therapy trials for hemophilia A and B are utilizing 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]. While 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]. While AAV is predominantly a non-integrating virus, integration events demonstrated in large animal and humans, post AAV gene transfer occur at an estimated frequency of at approximately 0.1% per transduced cell [4,7,9]. Hepatocellular carcinoma (HCC) was seen in one liver directed rAAV preclinical murine study [10]; a larger study found that HCC risk depended upon vector dose, promotor, enhancer and the degree of hepatic cell division during vector administration [11]. A 10 year follow up of AAV-mediated 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 post-intravascular 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 over 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 three years 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 X 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 preclinical 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 to AAV-mediated gene therapy and post-marketing 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 co-medications, 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 FDA of 5 years [17].

The World Federation of Hemophilia (WFH), working with the International Society of Thrombosis and Hemostasis (ISTH), along with the European Haemophilia Consortium (EHC), the US National Hemophilia Foundation (NHF), the American Thrombosis and Hemostasis Network (ATHN), industry developer partners and regulatory liaisons, is developing a global gene therapy registry. This registry will utilize a core data set, with input from a multi-stakeholder steering committee. Guidance from the U.S. FDA and European Medicines Agency have 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 Supplemental Table 1. The aim of the gene therapy registry project is to provide a core data set integrated

into a robust, scientifically valid registry, 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.

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 post-regulatory 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 in order to account for potential selection bias in enrollment. Clinical trial participants will be enrolled following the closure of their trials, and post-approval PWH will be enrolled at the time of vector infusion.

Wide-spread 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 (HTC)s 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 post-registration as well 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.

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Role and contribution of each author

DC 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. BAK, GFP and DC drafted the first manuscript which was critically evaluated, edited and approved by all authors.

Conflict of Interest Disclosure

BAK, GFR, DC, MN, CC, LAG, AI, BOM, SP, MWS, CW, FP, JNM have declared no conflict of interest

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Table 1. Summary of Key Areas of Core Data Collection for gene therapy*

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

*See Supplemental Table 1 for full Core Data Set