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COMMENTARY

Gene therapy to cure haemophilia: Is robust scientific inquiry the missing factor?

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Haemophilia, a rare inherited bleeding disorder, is caused by a defect in the factor VIII (FVIII) (haemophilia A) or factor IX (FIX) (haemophilia B) gene leaving people with haemophilia (PWH) at significant risk of spontaneous bleeding and resultant severe pain, joint disease, disability and premature death.[1] From our earliest memories, we, all men born with severe haemophilia, have dreamed of a cure. We witnessed many false starts beginning in the 1990s through the 2000s[2] until the first hint of effectively ameliorating our phenotypes appeared.[3] Development of the FIX Padua mutation, offering five-fold to sevenfold higher specific activity, and recent FVIII trials have allowed the possibility that the severe haemophilic phenotype really could be changed to mild or even normal.[4,5]

The biology of introducing adeno-associated virus vector (AAV) delivering a coagulation factor into humans has fallen far behind the phenomenologic changes in phenotypes. With gene therapy, a change from severe to mild or normal phenotypes is a major accomplishment but a discriminating review of the data is unsettling. A framework of known unknown questions has been developed,[6] which remain largely unanswered[2] despite the fact that large-scale clinical trials are moving towards completion.[7]

The authors of this article were all born with severe haemophilia and are widely published in the field and frequently lecture on related topics. They are and have been leaders at national and international levels including the World Federation of Hemophilia, European Haemophilia Consortium, Irish Haemophilia Society, Canadian Hemophilia Society, National Hemophilia Foundation (US) and Polish Hemophilia Society. One of us was cured of haemophilia through a liver transplant for end-stage HCV-induced cirrhosis, one was recently treated with a gene therapy vector and is now free of clotting factor concentrate usage, and the other four are patiently waiting to make the commitment to seek a cure. Most of us have been through the infectious disease wars, as patients, advocates, activists and self-treaters.

For the first time in haemophilia, a core outcome set for gene therapies has been developed (coreHEM) with the involvement of patients, clinicians, researchers, drug developers, regulators and payers.[8] Patient involvement ensured that efficacy outcomes were both meaningful and relevant to those living with haemophilia. Core outcomes also include safety events required as per good clinical practice and regulatory guidance, including liver toxicity, immune responses to transgene and capsid, thrombosis, development of other disorders, vector integration into host genome, duration of vector-neutralizing responses and cause of death. These efficacy and safety outcomes were relevant when they were adopted and remain so as gene therapy nears the market. In our view, circulating factor level is the key determinant in the success of gene therapy.[9]

Regarding safety, mildly elevated transaminases have been largely dismissed because the increases are mostly transient. This ignores the cause and whether there is ongoing low-level liver damage, analogous to what our community has seen with hepatitis C.[10,11] Are we taking AAV-induced liver inflammation as seriously as a 'one-and-done therapy that cannot be withdrawn' should dictate? Safety considerations are once again paramount with the very recent report of the deaths following liver complications of two children on an AAV gene therapy trial (AT132) for X-linked myotubular myopathy.[12]

Another safety aspect largely discounted [13] is low-level AAV integration. While significantly less efficient at integration than lentiviruses or retroviruses, given the trillions to quadrillions of vector genomes dosed, millions of integrations into the liver (and elsewhere) nevertheless occur.[14] Additionally, no data have been published about the possible impact on an innate immune response

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of an adventitious virus (Sf-rhabdovirus), which persists in insect cell lines used to manufacture some AAV vectors.[15]

When there is a lack of scientific consensus, we should not allow a rush to commercialization to unduly influence decisions. Where there is known uncertainty, such as integration, foundational research should be undertaken. The HIV epidemic in PWH analogizes our concerns regarding decision-making[16] and the precautionary principle. We recognize that uncertainty is unavoidable; some questions cannot be fully answered premarket. The numerous uncertainties, however, highlight the importance of a global longitudinal surveillance registry to capture outcomes for all PWH undergoing gene therapy.[17,18]

Clotting factor levels considerably above the upper normal limits of 150 IU/dL were observed in some patients in some FVIII and FIX studies.[5,19,20] This calls into question reliability and variability, and underscores the importance of full safety data disclosure by all sponsors. All haemophilia gene therapy trials have had participants at the low and high ends of response, with ranges of sixfold to >10-fold. Identifying the causes of inter- and intra-individual variability has not been a research priority, yet finding root causes of the variability might permit potential mitigants to be identified. Mitigation would include searching for interventions ranging from AAV manufacture to vector infusion to final protein secretion from the hepatocytes.

Variability may or may not be related to durability. Published FIX data suggest stable expression for at least 8 years.[21] Canine data for FVIII suggest stable lifetime expression. A human trial, however, shows a loss of FVIII from the end of year 1 to year 4.[22,23] Other sponsors have released no long-term data. Much more research is needed to understand the reasons for this decline. Decreases in bleeding and factor utilization will follow rises in clotting factor activity, and thus, FVIII or FIX activity is a quantitative discriminant for gene therapy success.[8,9] Since factor levels are dropping in some individuals, there has been a movement to disregard the levels and look only at bleeding rates and factor usage. This is a revisionist and unacceptable solution to establishing efficacy of gene therapy.[8]

These issues demostrate that the knowledge of the biology of AAV gene therapy has not kept pace with advancing clinical studies.[2] We ask, do we have a safe, reliable product to give us the sustained cure we are awaiting? Perhaps, not quite. Our expectations are mismatched to the reality of the available data. Unresolved issues make the decision of whether or not to undergo gene therapy difficult for the PWH:

- Knowing this new world does not include those seropositive from prior natural AAV infection (eligibility).
- What factor level one will achieve (reliability, variability).
- Not knowing how long expression will last (durability).
- Whether the result will make one independent of clotting factor (quality of life, transformational independence, resource requirements).
- The likely inability to take a second AAV gene therapy if first dose is inadequate (redosing).
- The impact of both liver inflammation and integration (safety).

Ethical considerations both premarketing and postmarketing, including robust education and discussion of the knowns, unknowns and alternative treatment options before or after gene therapy remain of paramount importance. The informed consent process, and process once these products are marketed, should include a well-structured framework of shared decision-making between healthcare providers and patients.

This is an urgent reminder while gene therapy is under clinical investigation. We need more transparency from all those pursuing clinical trials, including meaningful research on the unanswered questions around safety, variability and durability of response. Only in this environment, we can have confidence in this technology. A global registry is a vital and necessary foundation for tracking safety and efficacy,[17,18] but observational studies alone do not substitute for scientific investigations to further our biologic knowledge of this new and promising therapeutic modality.

DISCLOSURES

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