GENE THERAPY

Patient advocacy helps patients weigh up gene therapy trial risk/benefits

John Morris

The investigators behind the first gene therapy trial with adeno-associated virus 8 (AAV8) Factor IX appointed a patient ombudsperson to help ensure participants were able to give truly informed consent. The experiences and challenges of the ombudsperson, who met with the first six UK-based patients, are described. It was stressed to potential participants that altruism, rather than any expectation of clinical benefit, should be the primary motivation to taking part. At the same time a sober assessment of the potential risks to their safety needed to be made.

Key words: haemophilia, haemophilia B, Christmas Disease, gene therapy, factor IX, informed consent

It is a well-worn cliché, but still a good one, that a life-long cure for haemophilia through gene therapy is the Holy Grail of treatment. This applies to patients as well as healthcare professionals. While working as a patient information and support professional with the UK's Haemophilia Society, patients and carers often asked me when they should expect gene therapy to become a routine part of treatment and care. The standard answer throughout the haemophilia field has always been that it was 5 to 10 years away, depending upon whether you were an optimist or a pessimist. Disappointingly, the answer has remained the same for 20 years or so: a genetic cure is still 5-10 years away. However, recent successes in an ongoing clinical trial with patients with severe haemophilia B that began at the Royal Free Hospital, London [1,2], has made that question much more pertinent, and those answering it need be far less coy.

In 2008, after seven years' work in haemophilia patient charities, I was invited to be the 'patient ombudsperson' or 'research participant advocate' in the first clinical study with the adenovirus-associated virus 8 (AAV8) vector. In UK clinical trials these terms were virtually unheard of, but the potential risks of this experimental treatment surely merited such a position. I was able to contribute an unusual combination of experience in patient advocacy and knowledge of haemophilia care, as well as counselling and training skills.

The Gene Therapy Advisory Committee (GTAC) is responsible for granting ethical approval for gene therapy trials in the UK. Before the trial received its go-ahead, I had been asked to speak at a GTAC meeting about the

John Morris, Patient Advisor, Katharine Dormandy Haemophilia Centre & Thrombosis Unit, The Royal Free Hospital, London, United Kingdom
Email: jmorris@tinyworld.co.uk

For participants in a gene therapy trial, informed consent required piecing together a thorough understanding of the potential risks to themselves and benefits to the wider haemophilia community

Haemophilia Society's view of gene therapy research and experience of current best treatment and care. Our answer was quite simple: we supported research into better treatment and care for people with haemophilia, provided there were adequate safeguards in place to minimise harm to patients, and that those participating were fully aware of what they were letting themselves in for. We did not support the view that twice-weekly self-infusion with factor IX concentrate was the be-all and end-all of treatment for haemophilia B; an alternative was still keenly sought.

At that meeting I expressed concern about the small recruitment pool — participants needed to be adults, have severe haemophilia B, have the 'right' mutation, no ongoing viral hepatitis or HIV infection and of course a willingness and availability to take part. The disaster of HIV and hepatitis C transmission through contaminated blood products, which themselves were once heralded as ground-breaking new treatments, was all too well known,

and called for absolute caution when trialling new therapies and mitigated against patient enthusiasm. On the other hand, patients at the larger UK treatment centres were used to being asked to take part in research for new clotting factor preparations and treatments for hepatitis C, and were often willing to put themselves forward. There was always a danger that they would not appreciate anything particularly different with gene therapy, and, with absolute trust and respect for their doctor, blithely enter the trial with little appreciation of the possible consequences. Such naivety was something I had witnessed in helpline service users who were being treated with pegylated interferon and were unaware that it was unlicensed and therefore experimental.

In broad terms my brief was to ensure that patients understood the possible consequences of participating. In the earliest stages, the trial's mantra was that no-one should expect any therapeutic benefit — the primary objective of the phase I trial was to assess the safety of the intervention. The AAV8 vector had been designed to minimise harm, but injury could not be ruled out. The most serious risks — of developing cancer or an inhibitor to the factor IX protein, or of germline transmission — could not be quantified and remained theoretical, but nevertheless needed to be considered. Based on the experience of previous clinical trials, the most likely side-effect was an immune response to the vector, manifest as liver inflammation. A guaranteed negative outcome of participation was the inconvenience of the hospital stay after infusion and a string of return visits for blood tests; in practical terms a lifetime of monitoring.

The only valid motivation

The one certain positive outcome was the satisfaction of contributing to medical research. Whichever way the results went, every single patient would make a remarkable contribution to knowledge about gene therapy. At an open meeting for patients to learn about the trial and begin thinking about taking part, I majored on altruism as the only valid motivation for taking part. A handful of people contribute to medical research by making a fortune and giving much of it away; plenty more collect sponsorship money for research charities by achieving unenviable feats of endurance. But if ordinary people wanted to make their own very extraordinary and valuable contribution to haemophilia research, they need 'only' put themselves forward for this trial.

My task was best summarised as ensuring patients were giving truly informed consent to joining the clinical trial. I always spent around an hour discussing participation with patients in private surroundings, before they were asked to sign the consent form. Simply put I was to be their 'friend' — someone outside the clinical team whose foremost concern was to explore with them the pros and cons of taking part, ensuring they had the space to talk through their thoughts, feelings and concerns about participating. It was vital that I was genuinely independent, with no financial interests that might compromise my neutrality. This did not mean that I was the sole and final arbiter of authentic informed consent; I could only advise the clinical team if I thought someone had not taken it all in. That said, they would be extremely unlikely not to take my advice and proceed with the patient regardless.

One member of the clinical team once semi-jokingly suggested that my job was to convince a potential participant that he should not take part. In reality I remained non-directive, but I took the ambiguous gesture as a genuine expression of the investigators' desire not to recruit anyone who had not properly appraised the risks to his health. In the event, none of the six first-round participants who completed the preliminary eligibility tests changed his mind about the research. Some appreciated the chance to explore their feelings about the possible risks with me, while others used the opportunity to enhance their knowledge about the specifics of the trial and its wider context. Our conversations often generated questions to refer back to the clinical team, as I did not have the clinical experience or medical knowledge to answer every query.

On a handful of occasions I spoke with people who were only just beginning to contemplate taking part, and for some this confirmed in their minds that the trial was not for them. One man decided the risks were too great. Another queried whether as an "ex-haemophiliac" he would continue to receive the first-rate level of care for co-morbidities arising from joint damage that he currently enjoyed from his haemophilia treatment centre. A further more philosophical question arose: how would an individual feel about losing his identity as someone with severe haemophilia B, and his cherished long-standing relationships with his haemophilia clinical team as well as his patient community?

Tangible challenges

Other challenges I faced were much more tangible. I anticipated a dilemma over what position in the treatment sequence a patient might take, given the choice. Wouldn't the hardest thing be to go first — to be the first ever human to try the treatment, even at the lowest dose? Far better, surely, to be the next person in line for a dose that had been used before. And which of the three doses might someone choose? As the quantity of vector increased so would the potential for greater clinical benefit, while at the same time so would the potential for harm.

Related to this dilemma was that treatment with the AAV8 vector would render it impossible to use again, because the patient's immune system would invariably mount a successful attack on any subsequent re-introduction of the vector. Far from research patients feeling at the head of the queue for a promising new treatment, they would actually cast themselves to the back of it, waiting for a different vector to be commercialised

and become the treatment of choice. Anyone aiming for gene therapy with the AAV8 vector to grant useful expression of factor IX would want the highest dose, as he only had one stab at it.

Beyond the possible side-effects, none of these additional facets deterred anyone from taking part. Moreover, as far as I could tell, their altruism meant they were happy to take their allocated place in the testing sequence. Those with family connections to haemophilia could give a personal focus for their commitment — they were doing it for their carrier-daughter wanting a family, or for an affected nephew or grandson.

A vital part of any ethical consenting process is affirming the right to withdraw from the trial at any point. However in this trial, once the vector has been introduced into the body, it would be extremely unwise to pull out of the ensuing observations and investigations. Consequently, at the point of infusion my role effectively ended. I made myself available to any patient who might need further support or advocacy, but this offer was never taken up, even after the initially alarming episodes of liver inflammation at the highest dose.

I dedicate this article to the six UK-based men that took part in the first stage of the AAV8 gene therapy project. I hugely admire their altruism and acknowledge their immense contribution to advancing this science. As the work progresses and the risk–benefit considerations become better understood and managed, I hope the importance of my advocacy role will diminish until it is no longer needed. A far more vital observation is that the promise of gene therapy becoming the mainstay of haemophilia treatment in the next 5-10 years can now mean exactly that, and no longer be pushed further into the future.

Disclosures

The author has advised that he has no interests that might be perceived as posing a conflict or bias.

References

1. Nathwani AC, Tuddenham EG, Rangarajan S, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med* 2011; 365: 2357-65. doi: 10.1056/NEJMoa1108046.
2. Nathwani AC, Reiss UM, Tuddenham EG, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med* 2014; 371: 1994-2004. doi: 10.1056/NEJMoa1407309.