Gene therapy

Gene therapy for haemophilia has been in advanced clinical trials for some years now and this Congress was a timely forum to discuss and evaluate it critically.

Robyn Shoemark

Plenary: Perspectives on curing hemophilia

Speaker ~ Mark Kay, Professor of Pediatrics and Genetics, Stanford University School of Medicine, USA

In his plenary presentation *Gene therapy for haemophilia - Where are we towards a cure?* Professor Mark Kay outlined the progress in gene therapy to date, what's in the pipeline and some key questions for the future.

Since the 1980s there has been a lot of progress and, more recently, clinical success in gene therapy.

Virus vectors engineered in the laboratory have evolved to become efficient carriers to deliver gene therapy in humans. The AAV (Adeno-associated virus) vector has been found to be effective in delivering the sequences needed in gene therapy for haemophilia.

In the first haemophilia B gene therapy trials there was a T-cell response causing transaminitis (high levels of certain liver enzymes called transaminases) and expression of factor IX waned. In the clinical trials that followed, steroids were used and helped to reduce the transaminitis.

Mark then went on to discuss gene therapy clinical trials for both haemophilia A and B. In future we can expect to see gene therapy involving genome editing technology, with directed changes to the host's DNA sequences, and other different types of gene therapy. Watch this space.

A significant hurdle to overcome in future trials is the differences between animal and humans. This includes dosage, expression and safety. Mark posed a number of questions:

- How do we predict human outcomes? There is variability in individual dosing and immune responses.
- Are we targeting the correct cell types in the liver? Hepatocytes vs liver endothelium.
- What is the risk for cancer? Oncogenesis, or the process where normal cells turn into cancerous cells, is likely a low but not an absolute zero risk.

Where are we going from here? Mark concluded there is room for improvement in AAV vectors, along with new vector possibilities. Genome editing with gene transfer technologies is in the pipeline. Gene therapy may result in lifelong expression from neonate to adult, with the possibility of reinfusion to 'fine-tune' dosing.

Late-breaking Clinical Research

Chair ~ Glenn Pierce, Vice President Medical, World Federation of Hemophilia, USA

Immune suppression following gene therapy in hemophilia

~ Wolfgang Miesbach, Leiter Schwerpunkt Hämostaseologie/Hämophiliezentrum, Universitätsklinikum Frankfurt, Germany

Wolfgang Meisbach discussed some of the immune complications of gene therapy for haemophilia A and B and their implications. He highlighted that patients need to be aware of both the risks and benefits before undertaking these therapies. Known complications include transaminitis and cellular immune responses. This is seen in the form of raised AST/ALT (liver function) and IgG (Immunoglobulin G antibody) results which can be treated with corticosteroids.

There are still many differences in clinical trials and their outcomes, including variability in factor levels. How appropriate is gene therapy for an individual patient? It is important to weigh up the risks vs benefits to decide what is right for the patient and if a trial is indicated for them. >>

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Gene therapy continued

Suzanne O'Callaghan

Plenary: Gene therapy - are we ready now?

Speaker ~ Radek Kaczmarek, Postdoctoral Research Associate, Gene and Cell Therapy Group, Wells Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, USA

In a thoughtful but challenging presentation, Radek Kaczmarek continued the discussion about the current gene therapies for haemophilia A and B that use AAV vectors to transfer the gene. He explored the concerns about efficacy and safety and the pathways to lessen the side-effects and find solutions to these issues, including for those who are as yet unable to receive gene therapy.

He commented on some current concerns:

- High liver responses in some patients
- More durable response in haemophilia B gene therapy than haemophilia A.

Most patients who received gene therapy have shown an increased factor level and have remained off replacement factor therapy. However, the variability in factor levels is a concern as those with suboptimal levels cannot have a repeat dose for 15 years.

He also proposed that there needs to be much more discussion about the ideal target factor level range for gene therapy. For example, factor levels over 15% virtually eliminate joint bleeds.

In conclusion, he argued: 'Overall the causes and mitigants of wide variability, waning efficacy in the case of haemophilia A and liver toxicity have not been sufficiently studied.

'Due diligence around uncertainties will be critical for people with haemophilia, who have endured a difficult safety legacy and failed hopes. Ideal gene therapy for haemophilia will ultimately close the gap between how much haemostatic correction the therapy can provide and how much is needed to provide a life independent of treatment. The current state of the art brings us close to this goal, but getting there will involve more time and innovation.'

Please note that the Congress reports above represent the views of the Congress speakers.

At the time of publication gene therapy for haemophilia is available through clinical trials. Some advanced clinical trials are promising and some gene therapy treatments may well reach the global market in the next year or so if they pass the required regulatory hurdles.

If you want to know more about clinical trial opportunities for you, it is recommended that you speak to your Haemophilia Treatment Centre doctor.

Suzanne O'Callaghan is HFA Policy Research and Education Manager.

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