**Gene Therapy in Haemophilia**

There has been considerable chatter for many years about gene therapy being a potential cure for Haemophilia. This reached fever pitch in June 2022 with the European Medical Agency granting conditional marketing authorisation for *Roctavian* which is a gene therapy for Severe Haemophilia A. We wanted to take some time to cut through the noise and explore exactly how potential gene therapies for Haemophilia work and how realistic that it is for them to provide a widespread ‘cure’ in the future.

**How Gene Therapies Work**

Every person’s genes contain the instructions for how to make proteins, the chemical building blocks out of which the human body is made. In people with haemophilia (PWH) the gene to make one of the clotting factors is absent or broken which means the body cannot effectively make this key protein for blood clotting. In Haemophilia A the gene for factor VIII is affected and in Haemophilia B the gene for factor IX is affected. Gene therapy is given as an intravenous injection, not unlike taking factor injections. The gene therapy itself is a specially modified virus, known as a vector. These modified viruses are specially programmed to insert a functioning factor VIII or IX gene into a person’s cells and as a result a person’s liver can begin to produce its own fully functioning factors again. It is important to note that these viral vectors have been specially modified to be harmless and are non-infective. Many people post gene therapy can achieve normal factor VIII/IX levels which means they no longer develop bleeding complications or require factor replacement injections. Although the exact factor levels people achieve after gene therapy is highly variable.

**Potential Limitations**

This all sounds very simple, but gene therapy is not without potential challenges. Adenoviruses, on which most gene therapies are based, are very common and spread by droplets causing coughs, sneezes, and sore throats. As a result some patients will already have many antibodies against the gene therapies which are based on adenoviruses, and the gene therapies will be ineffective.

Even if patients do not have pre-existing anti-bodies to begin with, the immune system still can react against cells in the liver where the gene therapy has worked. This can cause some inflammation of the liver in the short term, which is usually managed by steroids. Generally patients have no symptoms of liver inflammation, and it is only detected on blood tests, however if the inflammation is not controlled it can cause the treatment to stop working.

Over the longer term, the cells making the factor are slowly destroyed meaning factor levels fall over time. Some patients eventually have to go back on to factor replacement therapies again as a result. To date long term follow up of patients after receiving gene therapy is lacking, so we do not know how long the gene therapies will last for before patients have to go back on to factor replacement therapy. We urgently need more of this long term data so that patients can make informed decisions.

**Conclusion**

Overall, clinical trials look very promising for gene therapy in Haemophilia. The concept definitely works; however it remains to be seen how long these treatments are effective for. It is expected that market authorisation for *Roctavian* will be granted soon in the UK and many other gene therapies are also in advanced stages of clinical trials for both Haemophilia A and B.

If you wish to learn more about gene therapies, the European Haemophilia Consortium produces some excellent resources and videos about gene therapy. These can be found at <https://www.ehc.eu/ehconversations-gene-therapy-series> .