Patient considerations for potential AAV gene therapy for Gaucher Disease type 1

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Background

Gaucher disease type 1 (GD1) is a rare genetic lysosomal storage disorder caused by mutations in the *GBA1* gene, resulting in deficient glucocerebrosidase (GCase) and impaired breakdown of glycosphingolipids.[1]

- This deficiency leads to the accumulation of glucosylceramide and its toxic metabolite, glucosylsphingosine (lyso-Gb1), in multiple cell types.
- While enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are currently standard of care for the treatment of GD1 patients, significant unmet need remains.[2-6]
- Clinical trials for AAV gene therapy in GD1 are underway; if an AAV gene therapy product were to become commercially available, physicians and patients would need to consider new aspects of their care, as the treatment model may change considerably.

AAV gene therapy for GD1

The goal of adeno-associated virus (AAV) gene therapy is to provide a long-lasting treatment with a single infusion that delivers a functional *GBA1* gene which will enable the body to produce fully active GCase.

- Patients would, therefore, no longer need to take their current ERT or SRT therapy.

Currently there are no approved gene therapy treatments for GD1, which means the only way to access gene therapy is by taking part in a clinical trial.

- Trials offer an opportunity to receive an investigational treatment, while also supporting progress in scientific research that may help others with the disease in the future.
- Some patients will not meet the criteria to receive gene therapy.

Gene therapy overview

Gene therapy has the potential to change the treatment of many disorders.

- Gene therapies work best on genetic conditions caused by a change to a single gene (monogenic) e.g. Gaucher disease.

Current gene therapy trials for GD1 provide a working copy of the *GBA1* gene into a patient's cells. This method can be used if a gene change is preventing cells from making enough of a certain protein. For gene therapies being delivered by an AAV vector, the working gene does not alter a person's current genetic make up.

Several gene therapies have already been approved in other disease states such as haemophilia A and B, spinal muscular atrophy and sickle cell disease.

Possible areas of impact to the current Gaucher treatment model that would need consideration *

Access

- Based on where people live and the status of health systems, access to therapies can be challenging. A single infusion of a gene therapy may be more readily accessible in some places than long-term challenges with ERT coverage. Conversely, some countries and plans may not provide coverage for gene therapies at all.

Efficacy

- While it is hoped that gene therapy will offer similar or potentially even better clinical outcomes than existing GD1 treatments, there is no guarantee that this will be the case. Clinical studies are being run now to determine this.
- Early trial data suggests that gene therapy may be beneficial in reducing fatigue, pain, and bone pathology over what has been seen with standard of care (SoC) while maintaining the benefits attained with SoC including normal levels of hemoglobin, platelets, and organ volumes.

Convenience

- AAV gene therapy is meant to be a single infusion with lasting effects, removing the need for further chronic ERT or SRT use. Some patients, however, have become accustomed to the routine of biweekly interactions with ERT infusion staff.
- For patients that have been on long term treatment and have infrequent follow up visits, these follow up visits will need to be more frequent over the first months after gene therapy.
- A patient's current treatment centre may not have the capabilities to deliver gene therapy. Therefore, delivery of a gene therapy may have to occur in another facility with follow up at their current centre.
- Currently, there are less than 50 centres worldwide that are trained on providing gene therapy for GD1. With an approved product, training for additional centres would be required.

Involvement in clinical trials

- Being a part of a clinical trial allows patients earlier access to an experimental therapy, but they do require a time commitment that many people may not feel they can manage. By their nature, trials carry the chance that it does not work, and prior therapies need to be restarted.
- Any patient that is in a trial can decide to exit the trial at any point, although there is no way to withdraw the gene therapy.
- Some patients may enjoy the extra visits and assessments received over the course of a trial and are excited about the prospect of a potential one-and-done therapy; this will need to be weighed against the knowns of current care.

Lifestyle

- Without the restrictions of planning for ERT infusions every 2 weeks, patients may be able to make lifestyle changes such as travelling for longer periods or moving abroad. With this, new considerations for ongoing patient check ins may need to be considered if they are traveling or have moved.

Eligibility to receive gene therapy

- Not all patients would be eligible to receive gene therapy given their past exposure to AAV or their immunological environment.
- Discussions on treatment options would need to expand to include screening requirements and expectation setting on eligibility for access.

Durability

- Whilst it is hoped that the gene therapy treatment will last for many years, currently it is unknown exactly how long that will be. Data on durability past 5 years may not be available at the time of any commercial availability.
- As of today, receiving a second "top up" dose of a gene therapy is not possible although research is looking into this.
- Physicians and patients may need to consider the possibility of restarting ERT/SRT at some point in the future.
- Centres would need to consider changes to follow up plans to take this into consideration.

Safety

- The side effects of AAV gene therapy seen in clinical trials for GD1 are fairly mild, but we are still learning and the complete picture is not yet known.
- Immune reactions and the potential side effects of treatments to minimize these are of importance in gene therapies (please see immune response box for more information).
- AAV gene therapies for GD1 delivered into the blood stream (i.e., intravenously) have a lower likelihood of developing long term complications as the new genetic material does not integrate into the existing gene (reducing the risk of cancers), is not taken up by other cells across the body (reducing the risk of "off target" impact) and does not interact with dividing reproductive cells.
- Long-term data in AAV gene therapy trials in other diseases has not shown any increased risk of cancer.
- The total dose that a person receives of a gene therapy is considered a major component of the product's safety profile[7].
- The AAV vectors are cleared quickly from the body once they deliver the *GBA1* gene.

Immune response

- Mild elevations in liver enzymes have been seen, demarking the immune response to the AAV gene therapy. To date, these elevations have been managed with corticosteroids, although a full understanding will require additional data.
- A course of oral corticosteroids would often be utilized to ensure that the benefits of gene therapy take and last. There are side effects associated with these that would need to be discussed with the patient.

Conclusion

If approved, there would be many new factors for physicians and patients to consider in determining if gene therapy is the right choice. While we have attempted to anticipate some of these factors# above, patients will have many questions to which all the answers may not be known right now. It is important for patients to discuss these with their healthcare team along with family and friends to make sure they have the information they need to make an informed decision. Patient support groups would also play a vital role in providing further information and support as well as being able to help connect patients with other patients who are facing similar decisions.

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* This is not an exclusive list of all the considerations; patients would need to consult a health care professional for a full explanation of the risks and benefits associated with gene therapy.
# Anticipated factors are based on commonly raised themes by expert gene therapy groups such as ASGCT and ESGCT.

References: 1. Stirnemann J, Belmatoug N, Camou F, et al. *Int J Mol Sci.* 2017;18(2):441. **2.** Gary SE, Ryan E, Steward AM, Sidransky E. *Expert Rev Endocrinol Metab*. 2018;13:107–118. **3.** Shayman J A. *Advances in Gaucher disease: basic and clinical perspectives. Future Medicine Ltd, Grabowski: London;* 2013; 240–256. **4.** Weinreb NJ, et al. *J Inherit Metab Dis.* 2013;36: 543–553. **5.**Wyatt K, et al. *Health Technol Assess.* 2012;16:1-543. **6.** Revel-Vilk S, et al. *Br J Haematol.* 2018;182:467-480, **7.** Au HKE, *Front Med (Lausanne).* 2022 Feb 9:8:809118.