Manchester Royal Eye Hospital
Genetic Ophthalmology

Information for Patients

Gene Therapy

What is Retinal Dystrophy?

A retinal dystrophy is a condition associated with reduced or deteriorating vision in both eyes which can affect a person's ability to see fine detail, side vision and the ability to see in dim lighting conditions.

Retinal dystrophy is not one single condition but the general name given to a wide range of eye conditions (for example, Retinitis Pigmentosa). 'Dystrophy' means a condition that a person is born with, 'retinal' means relating to the retina - the light sensitive film at the back of the eye.

Most retinal dystrophies are genetic. This means they are caused by a mistake in a person's genes and both eyes are likely to be affected. Often the gene mistake has been passed (inherited) from one or both parents. There are a number of different ways in which this can happen; sometimes a new gene mistake occurs for the first time in an individual within a family but can then be passed on to future generations. There are many different genes that can cause retinal dystrophy and they can be inherited (passed through families) in different ways.

What is RPE65?

One of these genes is called RPE65. This gene makes a protein found in the retina that is vital for sight. A faulty RPE65 gene causes vision to deteriorate and may lead to almost complete loss of vision. Genetic testing can determine if an individual retinal dystrophy carries a mutation in the RPE65 gene. Gene therapy treatment aims to put a normal copy of the gene RPE65 behind the retina of patients with a surgical injection. Since a mutation in RPE65 prevents normal vision, the delivery of a correct copy of the gene can help to improve vision and/or prevent any worsening.

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A faulty RPE65 gene can lead to particular types of the following 2 diseases: Leber Congenital Amaurosis (LCA) and Retinitis Pigmentosa.

Leber Congenital Amaurosis

Some retinal dystrophies are diagnosed early in life. This includes the most severe group of retinal dystrophies, termed Leber Congenital Amaurosis.

LCA affects about 1 in 80,000 and causes the specialised, light-sensing, photoreceptor cells at the back of the eye to stop working properly. Typically, symptoms start in early childhood and worsen over time. These include:

- Poor and declining peripheral vision (tunnel vision)
- Night blindness
- Shaking eyes (nystagmus)

There are several different forms of LCA, each caused by mistakes in different genes. A mutation in RPE65 causes one form of LCA.

Retinitis Pigmentosa

Some retinal dystrophies have changes in the appearance of the retina with an increased amount of pigment in the retina and are called 'Retinitis Pigmentosa' (RP). RP also causes night blindness and declining peripheral vision. RPE65 mutations have been found to be a rare cause of a diagnosis of RP.

What is Gene therapy?

Gene therapy is a new treatment which may be suitable for a small group of patients with retinal dystrophies caused by a fault in RPE65. In the past, there has not been any effective treatment for retinal dystrophies. Gene therapy for RPE65 has been developed and is now available in the US, UK and Europe. This treatment is called Voretigene neparvovec (Luxturna). It is likely that gene therapy will become available for other types of retinal dystrophies in the future.

How does Gene Therapy work?

Gene therapy is a very new treatment. It works by introducing a healthy copy of the faulty gene into the eye. The active substance in Luxturna (voretigene neparvovec) is a modified virus that contains a working copy of the RPE65 gene. After injection it delivers

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this gene into the cells of the retina, the layer at the back of the eye that detects light. This enables the retina to produce the proteins needed for vision. The virus used to deliver the gene does not cause disease in humans.

Some patients who had gene therapy treatment for RPE65 retinal dystrophy as part of a research study showed improvement in their ability to navigate a maze (a so-called 'Mobility test course') in dim light, as well as improvement in light sensitivity and visual fields. The effect was still seen at 5 years after the treatment. It is thought that having the treatment can stabilise a person's vision and prevent it getting worse. As with any treatment, there are risks (see below); including damage to the eye and/or that the vision would be worse after the treatment.

We don't yet know who may benefit most from gene therapy. The youngest patient in the research study was 4 years old; however, older patients in the study also reported some improvements after treatment. Some people did not find there was much improvement and others had some complications after the treatment. Therefore deciding when is the right time and who might benefit from this treatment is something the doctors will discuss carefully with you.

Deciding about treatment

Your doctor may have discussed possible gene therapy for you/your child if you have confirmed RPE65 retinal dystrophy; however, there are many further tests that are needed before the final decision can be made as to whether you/your child will be suitable for treatment. The doctor will meet with the geneticist and other professionals to look at the results of the tests before it can be confirmed if the treatment will be suitable.

The surgery for gene therapy

The gene therapy is given during a surgical operation called vitrectomy for which you/your child will need to have a general anaesthetic.

Vitrectomy is an operation to remove the vitreous, the transparent jelly behind the iris (coloured part of your eye) and lens, and in front of the retina (the light-sensing film at the back of your eye responsible for vision). The surgery involves making small incisions less than 1mm in the sclera (the white part of the eye) and then removing the jelly through fine instruments. Once the jelly is removed, Luxturna is injected under the retina using a very fine needle. The operation is completed by putting a bubble of air (sometimes gas) inside the eye, and closing the incisions with small self-absorbing sutures. The operation takes between 1 and 2 hours.

You will need to be given some medication (steroid tablets) before and after the surgery and will have eye drops afterwards. You will need to stay in hospital overnight and to lie flat on your back for 24 hours after the operation so that it will work correctly. You should not expect to see anything from the eye that has had the surgery for a couple of weeks, and then your vision should gradually return.

The air takes 1-2 weeks to get absorbed and during this time the eye will produce fluid called aqueous humour to replace the jelly. It is important that you do not fly whilst you have air (or gas) in the eye, since the bubble will expand during air travel leading to a dangerous rise in eye pressure which can result in complete loss of vision. You should also avoid swimming because of an increased risk of infection in the eye.

One eye is done at a time; the second eye can be done at a later stage if required. You will need to have a lot of clinic appointments both before and after the treatment. Small quantities of Luxturna may be in your tears for up to 14 days; therefore for the first 14 days after the treatment, you will need to put any waste material from dressings, tears and nasal secretions into sealed bags (which will be given by the hospital). You would have to bring the sealed bags to the hospital so that we can dispose of them. It is recommended that patients/caregivers wear gloves for dressing changes and waste disposal, especially in case of underlying pregnancy, breast-feeding and immunodeficiency of caregivers. Patients treated with Luxturna should not donate blood, organs, tissues and cells for transplantation. This is because Luxturna is a gene therapy product.

The effects of this medicine on pregnancy and the unborn child are not known. As a precaution, you should not receive Luxturna while you are pregnant, and should take contraceptive precautions.

What are the risks of the procedure?

The following serious side effects may occur during or after the gene therapy:

- Infection and bleeding in the eye. The risk of these occurring is very low but they can be very serious and can result in permanent severe visual loss.
- Permanent decline in visual acuity, or the sharpness of central vision.
- Changes in the retina (the thin layer of tissue in the back of the eye) that can lead to vision loss including:
    - Development of a hole or separation of layers in the centre of the retina; and thinning, loss of function or bleeding in the retina.
    - Retinal breaks, wrinkling on the surface of the retina or retinal detachment.

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- Inflammation in the eye triggered by surgery as well as the new gene in Luxturna. This is why patients are given a short course of anti-inflammatory (steroid) tablets and eye drops.
- Increased pressure inside the eye.
- Formation or worsening of cataract (clouding of the lens inside the eye).
- Tell your doctor right away if you have any of the following symptoms of these serious side effects:
    - Seeing floaters (specks that float about in your field of vision) and flashes of light.
    - Pain in the eye.
    - Any change in vision including decreased vision or blurred vision.

What to expect after the surgery

- Expect your vision to be blurred for a few weeks after surgery.
- Expect your eye to be sensitive, swollen and red due to the nature of the surgery. You will be prescribed a combination of eye drops to put in on your discharge home. These will help to prevent infection, reduce inflammation and rest the eye following surgery.
- You will be expected to lie flat on your back for 24 hours to increase the effect of the procedure and reduce the risk of complications.
- You will be an inpatient for one night (the night of the surgery) and you will be examined the following day. You will attend an out-patient clinic at the Manchester Royal Eye Hospital at 1 week and then at 1 month and 3 months after surgery where the doctors will examine you and discuss your progress. Further appointments may be necessary.

Please remember that each patient is different and the information contained in this leaflet is only a general guide. For more information and support or if you require further advice relating to the information in this leaflet, please contact Ward 55 on (0161) 276 5512 staff are available 24 hours every day.

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