Voretigene neparvovec

Approved indication: inherited retinal dystrophy

Luxturna (Novartis)
vials containing concentrate for dilution before subretinal injection

Conditions such as retinitis pigmentosa are now known to be due to the lack of an enzyme in the retinal pigment epithelium. This enzyme (RPE65) is involved in the processes that convert light to an electrical signal. An enzyme deficiency mainly affects the rods, so patients lose peripheral vision and the ability to see in low-light conditions. There is continuing retinal degeneration, so most affected children become blind. As genetic mutations can cause the absence of RPE65, there has been research into the possible role of gene therapy for the inherited retinal dystrophies.

Voretigene neparvovec is engineered to provide a copy of the gene that codes for RPE65. It is delivered to the retinal pigment epithelium by the subretinal injection of a viral vector. One dose is given into each eye, but there should be a gap of at least six days between injections. Patients require immunomodulation with prednisolone before and after the procedure. DNA from the vector may be detected in tears for a few days after the injection.

The main study of voretigene was an open-label phase III trial involving patients with biallelic mutations of the RPE65 gene. These patients had a visual acuity of 20/60 or less, or visual fields less than 20° in any meridian. They were unable to pass a multi-luminance mobility test (MLMT) at a light level of 1 lux. Nearly half the patients needed a light level of at least 125 lux to pass the test. Their average age at randomisation was 15.1 years. A group of 21 patients was given subretinal injections under general anaesthetic while another 10 acted as a control group. Within one month patients given voretigene were better able to see in low-light conditions. After one year, 65% of these patients were able to pass the MLMT at 1 lux. There was little change in the control group. The best corrected visual acuity increased by an average of 8.1 letters with treatment compared with 1.6 letters in the control group.[1]

The results for these patients were reviewed after two years, along with the outcomes for those involved in phase I trials. Patients in the control group of the phase III trial had the option of having injections of voretigene, so a total of 40 patients have been reviewed. The improvements in the MLMT were maintained. Sensitivity to light improved across the visual fields.[2]

Most of the adverse events with voretigene were associated with the procedure, for example retinal tears and haemorrhage. Other events reported in the phase III trial include raised intraocular pressure, cataract and inflammation of the eye. There is a risk of endophthalmitis. The immunomodulatory regimen may reduce the immune reaction to the injection of a viral vector. As the vector may be shed, waste material, such as dressings, should be stored in sealed bags before disposal. Patients should not donate blood. They should also avoid air travel soon after the injection as the treatment will leave an air bubble within the eye. This dissipates over time.

Only a small number of patients will be eligible to be treated with voretigene neparvovec. They will need to have genetic testing to confirm that they have a biallelic RPE65 mutation. It is also a requirement that they have an adequate number of viable retinal cells. Treatment improves the patients' ability to function in low-light conditions and this may be sustained for four years.[2] The changes in visual acuity may not be significant, but if visual acuity remains stable this would be an improvement on the natural history of inherited retinal dystrophy. The patients in the trials are going to be followed up for 15 years[2] so the long-term effects of treatment will become clearer.

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REFERENCES

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

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