NEW DRUGS

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Onasemnogene abeparvovec

Approved indication: spinal muscular atrophy

Zolgensma (Novartis)
vials containing 2x10^{13} vector genomes/mL

Spinal muscular atrophy is an autosomal recessive genetic disorder. Mutations in the survival motor neuron (SMN) 1 gene lead to a deficiency of SMN protein. This results in the loss of motor neurons and therefore reduced muscle function. The severity of the disease depends on how much SMN protein can be produced by another gene (SMN2). In the most severe form of the disease, spinal muscular atrophy type 1 (SMA1), the infant is unable to sit upright and usually requires ventilation before the age of two years.

As there is no effective treatment for spinal muscular atrophy there has been research into gene therapy to correct the underlying disorder. Infusing a copy of the gene could increase concentrations of SMN protein. A phase I study tried gene therapy in 15 infants with SMA1. Following a single infusion of genetic material at 3–6 months of age, the infants' motor function improved. They were all still alive at 20 months of age and did not require permanent mechanical ventilation.[1]

Onasemnogene abeparvovec is a genetically engineered copy of the human SMN gene delivered by an adeno-associated viral vector. The dose is determined by the weight of the child and is given by intravenous infusion over one hour. The vector spreads through the body and is shed in saliva, urine and the faeces. Most of it is cleared within one month and the virus is not expected to cause infections.

An open-label phase III trial in the USA enrolled 22 babies (mean age 3.7 months) with SMA1. They had bi-allelic mutations of the SMN1 gene with one or two copies of the SMN2 gene. After a single infusion of onasemnogene abeparvovec, they were followed up until they were 18 months old. By this age, 59% (13/22) were able to sit for at least 30 seconds and 82% (18/22) did not require ventilation. One infant died during the trial.[2]

A similar trial in Europe treated 33 patients (mean age 4.1 months). By 18 months 44% (14/32) had been able to sit for at least 10 seconds and 97% (31/32) did not require ventilation. One infant died.[3]

Another open-label trial investigated giving onasemnogene abeparvovec to babies who were expected to develop spinal muscular atrophy. These presymptomatic babies had bi-allelic mutations with two or three copies of SMN2. They were treated before they were six weeks old. All of the 14 children with two copies of SMN2 were able to sit independently for at least 30 seconds by the age of 18 months.[4] The 15 children with three copies of SMN2 were all able to stand for at least three seconds at the age of two years and 14 were able to walk.[4,5]

Adverse reactions to onasemnogene abeparvovec are common. A review of safety data from several trials identified hepatotoxicity, thrombocytopenia, and cardiac adverse events as potential problems.[6] Liver function tests, platelet counts and troponin concentrations therefore require monitoring. To reduce the effect on liver function, prednisolone is recommended for 30 days, starting before the infusion. Patients are also at risk of immune reactions and thrombotic microangiopathy. Approximately half of the patients will develop a fever after treatment.

While the quantity of long-term data is limited by the rarity of the disease, the children from the phase I trial have now been followed up for five years. The 10 who received the therapeutic dose of onasemnogene abeparvovec all survived and did not require permanent ventilation.[7]

Although the outcomes for children given onasemnogene abeparvovec appear better than the historical outcomes in SMA1,[2,3] there is still substantial motor impairment. Patients who have already had irreversible damage to their motor neurons may be less likely to benefit from therapy. Experience in Australia with onasemnogene abeparvovec supports early treatment.[8] The Australian indication includes presymptomatic cases and the approval is restricted to infants under nine months old.

T manufacturer provided the product information

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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.