NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

Elivaldogene autotemcel for treating cerebral adrenoleukodystrophy

Final scope

Final remit/evaluation objective

To evaluate the benefits and costs of elivaldogene autotemcel within its marketing authorisation for treating cerebral adrenoleukodystrophy (CALD) for national commissioning by NHS England.

Background

Adrenoleukodystrophy (ALD) is a rare X-linked metabolic disorder in which accumulation of saturated very-long-chain fatty acids (VLCFAs) results in diffuse and multifocal demyelination (when myelin is damaged) of the nervous system and adrenocortical insufficiency. In ALD, the gene (ABCD1) responsible for the breakdown of fatty acids is faulty, causing damage to the adrenal glands, myelin, brain cells and the rest of the body[1].

As the disorder is caused by a faulty gene from the X-chromosome it almost exclusively impacts upon males, as they only have one X-chromosome. Females can be affected, but the likelihood is much lower as the presence of another unaffected X-chromosome mitigates symptoms and damage. ALD affects around 1 in every 17,900 males worldwide[2], or 1 in every 21,000 births[2], although estimates vary.

Cerebral adrenoleukodystrophy (CALD) is the most common form of ALD (around 45% of cases)[3], which usually affects male children and is characterised mainly by cerebral demyelination. Symptoms tend to present between the ages of 2 and 10[4]. When the myelin is damaged the nerves in the brain cannot work properly, and the person's functioning (such as reasoning, speech and mobility) are lost. ALD can be diagnosed after blood testing for high plasma concentrations of VLCFAs and additional blood tests may be done to confirm the ABCD1 gene mutation[5,6]. However, close monitoring is needed for the diagnosis of CALD as its early clinical symptoms are often misdiagnosed[4]. Progression of CALD is fast, symptoms worsen over the course of several months/years, leading to total dependency and eventually death[4].

Current treatment options for children with CALD are limited but can include stem cell transplantation, using either umbilical cord stem cells or bone marrow stem cells[5]. Stem cell transplant is considered in boys who have been diagnosed with the condition but in whom symptoms have not yet appeared, or if disease is not too advanced. Better outcomes are associated with stem cell transplants from matched and related donors[7].

The technology

Elivaldogene autotemcel (eli-cel, Bluebird bio) is a viral vector which is used in gene therapy. Haematopoietic stem cells with the CD 34 marker are taken from the patient's bone marrow. The vector is used to insert a healthy version of the disease-causing gene (ABCD1) into the stem cells which are then grown in culture. They are administered back to the body after myeloablative treatment (radio or chemotherapy). This gene addition aims to allow the production of functional adrenoleukodystrophy protein (ALDP), to potentially prevent further neurodegeneration. It is administered intravenously.

Elivaldogene autotemcel does not currently have a marketing authorisation in the UK for treating CALD. It has been studied in clinical trials in males aged under 18 years who have active CALD and do not have a willing 10/10 human leukocyte antigen (HLA)-matched sibling donor.

Intervention(s)	Elivaldogene autotemcel
Population(s)	People aged under 18 years with early cerebral ALD without a 10/10 HLA-matched sibling donor
Comparators	• Stem cell transplant • Best supportive care
Outcomes	The outcome measures to be considered include: • proportion alive without major functional disabilities (MFDs) • change in neurological function • time to subsequent allogeneic haematopoietic stem cell transplant • proportion who experience acute, chronic or worsening graft versus host disease (GVHD) • overall survival • adverse effects of treatment • health-related quality of life (for patients and carers)
Nature of the condition	• disease morbidity and patient clinical disability with current standard of care • impact of the disease on carer's quality of life • extent and nature of current treatment options
Clinical	• overall magnitude of health benefits to patients

Effectiveness	and, when relevant, carers • heterogeneity of health benefits within the population • robustness of the current evidence and the contribution the guidance might make to strengthen it
Value for Money	• cost effectiveness using incremental cost per quality-adjusted life year • patient access schemes and other commercial agreements • the nature and extent of the resources needed to enable the new technology to be used
Impact of the technology beyond direct health benefits	• whether there are significant benefits other than health • whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • the potential for long-term benefits to the NHS of research and innovation • the impact of the technology on the overall delivery of the specialised service • staffing and infrastructure requirements, including training and planning for expertise.

Other considerations	• if evidence allows, the following subgroups will be considered:
	  • People for whom a matched unrelated donor is available
	  • People for whom a matched unrelated donor is not available
	• guidance will only be issued in accordance with the marketing authorisation.
	• guidance will take into account any Managed Access Arrangements

Related NICE recommendations and NICE Pathways	None
Related National Policy	NHS England (2018), Manual for prescribed specialised services 2018/19 Chapter 100: Severe combined immunodeficiency and related disorders service (children) and Chapter 62: Highly specialist

	metabolic disorder services (adults and children) Department of Health and Social Care (2018) The UK Strategy for Rare Diseases. Second Progress Report from the UK Rare Diseases Policy Board NHS England (2017) Commissioning Medicines for Children in Specialised Services Department of Health (2016) The UK Strategy for Rare Diseases. Rare Diseases implementation plan for England NHS England (2018) National Programmes of Care and Clinical Reference Groups: E04. Paediatric Neurosciences NHS England (2013) 2013/14 NHS standard contract for paediatric neurosciences- neurodisability. Reference: E09/S/c Department of Health, The NHS Outcomes Framework 2016/17, (2016). https://www.gov.uk/government/publications/nhsoutcomes-framework-2016-to-2017

References

1. ALEX, the leukodystrophy charity. https://www.alextlc.org/what-is-a-leukodystrophy/the-different-leukodystrophies/adrenoleukodystrophy-ald/ (accessed October 2020)

2. Bezman L, Moser AB, Raymond GV et al. Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. Ann Neurol. 2001 Apr;49(4):512-7.

3. Stop ALD Foundation. http://www.stopald.org/what-is-ald/ (accessed October 2020)

4. Engelen M, Kemp S, Visser M et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. 2012; 7: 51.

5. Great Ormond Street Hospital for Children https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/adrenoleukodystrophy (accessed October 2020)

6. ALD Connect. http://aldconnect.org/education-and-support/what-is-ald (accessed October 2020)

7. Raymond GV, Aubourg P, Paker A, et al. Survival and Functional Outcomes in Boys with Cerebral Adrenoleukodystrophy with and without Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2019 Mar;25(3):538-548.