NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Exagamglogene autotemcel for treating sickle cell disease

Final scope

Remit/evaluation objective

To appraise the clinical and cost effectiveness of exagamglogene autotemcel within its marketing authorisation for treating sickle cell disease.

Background

Sickle cell disease is the name given to a group of lifelong inherited conditions that affect haemoglobin. The most common and often severe type of sickle cell disease occurs when people inherit a copy of the beta globin gene with the sickle mutation from both parents (homozygous sickle cell anaemia). Heterozygous sickle cell anaemia occurs when people inherit one copy of the beta globin gene with the sickle mutation from one parent and a different variant of the beta globin gene from the other parent. In all cases, the abnormal haemoglobin, known as haemoglobin S, tends to form polymers (or chains) with other haemoglobin S molecules. These polymers cause red blood cells to become rigid and misshapen, resembling a crescent (or sickle).[1]

Sickle-shaped red blood cells do not last as long in the body as regular shaped round red blood cells and get broken down more readily in a process known as haemolysis.[2] People with sickle cell disease often have anaemia because too much haemolysis occurs and there are not enough red blood cells to carry oxygen throughout the body. Sickle-shaped red blood cells also do not flow easily through the blood vessels and can cause blockages (vaso-occlusion) in different parts of the body.[2] Episodes of vaso-occlusion are known as vaso-occlusive crises. These lead to insufficient oxygen being delivered to tissues and organs, causing ischaemic injuries and excruciating pain (known as acute sickle cell crises). The frequency, severity and duration of these crises vary. Chronic complications caused by anaemia and sickle cell crises include progressive organ damage, fatigue and shortness of breath. Acute complications may also include acute chest syndrome, life threatening vaso-occlusive crises and stroke.[1]

It is estimated to affect 1 in 2000 live births[3] and there are approximately 18,000 people with sickle cell disease in England. People with sickle cell disease often have a reduced life expectancy[4] and it is estimated that in the UK, the median survival is 67 years.[5] The prevalence of sickle cell disease varies considerably across different ethnic communities, mainly affecting people of African or African-Caribbean family background, although the sickle gene is found in all ethnic groups.[6] The prevalence of the disease is increasing because of immigration into the UK, new births and increased survival.[7]

Sickle cell disease causes significant morbidity and mortality and usually requires lifelong treatment. Management in England includes education about the treatment and prevention of the acute and chronic complications of SCD. It particularly focuses on understanding when sickle cell crises occur and reducing the chances of experiencing a crisis by avoiding dehydration, sudden changes in temperature and

infection. Sickle cell crises may be extremely painful and will often require emergency admission to hospital and pain management with paracetamol, non-steroidal anti-inflammatory drugs and opiates. Hydroxycarbamide can also be used to improve anaemia and survival and reduce vaso-occlusive crises and some long-term outcomes. Also, it can be used to increase the production of foetal haemoglobin, which improves blood cell hydration and reduces red blood cell adhesion. This can reduce both acute painful crises and acute chest syndrome (caused by reduced blood flow in the lungs) in people with recurrent painful crises. Blood transfusions including exchange transfusions (where sickle red blood cells are replaced with healthy red blood cells) and simple (top-up) transfusions can help to maintain a healthy proportion of normal red blood cells to sickle red blood cells. They can also be used to treat acute complications and be given regularly to prevent disease complications. There are often complications such as iron overload and transfusions have associated risks such as blood shortages and lack of suitable donors. Allogenic stem cell transplant from a fully matched donor is the only currently available therapy that can cure sickle cell disease and may be considered,[7] but is not done often because of the lack of a suitable matched donors and the substantial risks involved.[9]

The technology

Exagamglogene autotemcel (brand name unknown, Vertex, CRISPR Therapeutics) does not currently have a marketing authorisation in the UK for treating sickle cell disease. It has been studied in a single-arm, open-label clinical trial in people with severe sickle cell disease aged 12 to 35 years who do not have an available human leukocyte antigen (HLA)-matched related haematopoietic stem cell donor. Severe sickle cell disease was defined in trials as having at least two vaso-occlusive crisis events per year for two consecutive years and documented severe sickle cell disease genotype.

Intervention(s)	Exagamglogene autotemcel
Population(s)	People with sickle cell disease
Comparators	Established clinical management without exagamglogene autotemcel including: • hydroxycarbamide • blood transfusions (exchange and top-ups) • best supportive care

Outcomes	The outcome measures to be considered include: • changes to haematological parameters (haemoglobin levels) • proportion of subjects who have not experienced any severe sickle cell crisis for at least 12 consecutive months • complications arising from sickle cell disease • proportion with and time to engraftment • mortality • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	**Related technology appraisals:** Crizanlizumab for preventing sickle cell crises in sickle cell disease (2021) NICE technology appraisal guidance TA743. **Related technology appraisals in development:** Voxelotor for treating haemolytic anaemia in people with sickle cell disease. NICE technology appraisal guidance [ID1403] Publication expected March 2021 **Related NICE guidelines:** Sickle cell disease: managing acute painful episodes in hospital (2012) NICE guideline CG143. Blood transfusion (2015) NICE guideline NG24.

	Related medical technologies: Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease (2016) Medical technologies guidance MTG28. **Related quality standards:** Sickle cell disease (2014) NICE quality standard 58 Blood transfusion (2016) NICE quality standard 138
Related National Policy	The NHS Long Term Plan (2019) NHS Long Term Plan NHS England (2019) Service specification no.18: NHS sickle cell and thalassaemia screening programme. NHS England (2019) Clinical commissioning policy: allogeneic haematopoietic stem cell transplantation for adults with sickle cell disease. Ref: 190138P Public Health England (2019) NHS sickle cell and thalassaemia screening programme standards Public Health England (2018) Sickle cell and thalassaemia: screening handbook NHS England (2018) NHS England funding and resource 2018/19: supporting 'Next Steps for the NHS Five Year Forward View' NHS England (2018) Manual for prescribed specialised services 2018/2019. Chapter 114 Specialist haemoglobinopathy services (adults and children). See: p.307 NHS England (2017) BI3 automated exchange transfusion for sickle cell care. Ref: QIPP 16-17 S28-B&I NHS England (2017) Next steps on the five year forward view NHS England (2016) Clinical commissioning policy: treatment of iron overload for transfused and non transfused patients with chronic inherited anaemias Ref: 16070/P Public Health England (2015) Sickle cell and thalassaemia screening: community outreach good practice NHS England (2014) NHS Five year forward view NHS England (2013) 2013/14 NHS standard contract for specialised services for haemoglobinopathy care (All ages) Ref: B08/S/a

	NHS England (2013) 2013/14 NHS standard contract for haematopoietic stem cell transplantation (adult). Ref: B04/S/a NHS England (2013) 2013/14 NHS standard contract for haematopoietic stem cell transplantation (children). Ref: B04/S/b

References

1. Nevitt SJ, Jones AP, Howard J. Hydroxyurea (hydroxycarbamide) for sickle cell disease. Cochrane Database of Systematic Reviews 2017, Issue 4 (Accessed May 2023)

2. Kato et al. 2018; Sickle cell disease, Nature Reviews Disease Primers; 4, 18010 (Accessed May 2023)

3. NICE (2021) How common is sickle cell disease? (Accessed May 2023)

4. Sickle Cell Anaemia (2023) BMJ Best Practice (Accessed May 2023)

5. Clinical Knowledge (2016) Sickle cell disease: prognosis (Accessed May 2023)

6. Clinical Knowledge (2016) Sickle cell disease: prevalence (Accessed May 2023)

7. NHS sickle cell and thalassaemia (SCT) screening programme (Accessed May 2023)

8. NHS England (2019) Clinical Commissioning Policy: Allogeneic Haematopoietic Stem Cell Transplantation for adults with sickle cell disease. (Accessed May 2023)

9. NHS, Sickle cell disease: treatment (Accessed May 2023)