Autologous CD34+ hematopoietic stem cells transduced ex vivo with lentiviral vector encoding for the human ADA gene for severe combined immunodeficiency caused by adenosine deaminase deficiency

NIHR HSRIC ID: 12511

Lay summary

Ex vivo lentiviral gene therapy is a new treatment for a type of severe immunodeficiency caused by lack of a specific enzyme, meaning the patient’s body is unable to fight infections. Current patients require stem cell transplants and regular injections of a replacement enzyme. Ex vivo lentiviral gene therapy modifies the patient’s cells to create the missing enzyme to potentially cure the condition.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.
TARGET GROUP

- Severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency.

TECHNOLOGY

DESCRIPTION

Autologous CD34+ hematopoietic stem cells transduced ex vivo with lentiviral vector encoding for the human ADA gene (ex vivo autologous lentiviral ADA gene therapy; OTL101; EFS-ADA gene therapy) is a novel therapy that is administered as a single intravenous (IV) infusion of 1-15x10^6 cells/kg body weight. Hematopoietic stem cells are harvested from the patient’s bone marrow, CD34+ cells are then purified and transduced ex vivo with a lentiviral vector containing ADA under the control of short form elongation factor-1a promotor (EFS-ADA). Transduced cells are then infused back into the patient. EFS-ADA lentiviral gene therapy is intended to treat children, adolescents and adults with ADA-SCID. In the phase II clinical trial, patients were infused with autologous CD34+ cells transduced with a lentiviral vector encoding ADA after non-myeloablative conditioning with busulphan1,2.

EFS-ADA lentiviral gene therapy does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, EFS-ADA lentiviral gene therapy will offer an additional treatment option for ADA-SCID that has the advantage of being a single treatment that may replace the need for allogeneic hematopoietic stem cell transplant (HSCT) and regular enzyme replacement with recombinant ADA. The company anticipates patients will be able to discontinue long-term IVIg due to B cell reconstitution, and require a shorter inpatient stay than currently required for allogeneic HSCT (21-28 days versus 45-90 days)a.

DEVELOPER

Orchard Therapeutics.

AVAILABILITY, LAUNCH OR MARKETING

In phase II clinical trials.

PATIENT GROUP

BACKGROUND

SCID describes a rare group of genetic disorders characterised by the absence of functional lymphocytes3,4 and very low levels of immunoglobulins of all isotypes resulting in severe and recurrent opportunistic infections3,5. SCID affects T lymphocytes, B lymphocytes and natural killer (NK) cells. It can be inherited in two ways; either X-linked or autosomal recessive2.

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*a Information from company
SCID due to ADA deficiency is transmitted in an autosomal recessive manner\(^3,5\). ADA is an enzyme involved in purine metabolism. ADA deficiency is caused by a mutation in the ADA gene (20q13.11)\(^5\), and leads to the accumulation of toxic metabolites that damage lymphocytes and result in severe lymphopenia\(^3\).

ADA-SCID is often diagnosed by age 6-12 months\(^6\). These children with early onset disease have failure to thrive and repeated opportunistic infections associated with marked depletion of lymphocytes and an absence of both humoral and cellular immune function\(^5,6\). If immune function is not restored, children rarely survive beyond their first year\(^5,6\). Delayed clinical onset affects about 10-15% of patients who usually present by 24 months of age\(^5\), while a smaller percentage present between 4 years of age and adulthood\(^5,6\). Typical features commonly include recurrent otitis media, sinusitis and upper respiratory infections\(^6\). Other symptoms may include extraintestinal manifestations, such as neurodevelopmental deficits, behavioural disorders, sensorineural deafness and skeletal and hepatic abnormalities\(^5\). Although infections in delayed- and late-onset types of SCID may initially appear to be less severe than those with severe early-onset disease, by the time of diagnosis these individuals often have chronic pulmonary insufficiency and may have autoimmune phenomena (e.g. cytopenias and anti-thyroid antibodies), allergies, and elevated serum concentrations of IgE\(^5\).

**CLINICAL NEED and BURDEN OF DISEASE**

Estimates for the incidence of all types of SCID range from 1.0-1.3 per 100,000 live births\(^7,8,9,10,11\); ADA-SCID is estimated to account for 15–20% of these cases\(^11,12,13\). Therefore, the annual incidence of ADA-SCID is estimated to lie in the range of 0.15-0.27 per 100,000 live births, or an estimated 1-2 patients per year in England (based on 664,399 live births registered in 2015)\(^14\).

In 2014-15, there were 101 admissions for adenosine deaminase deficiency (ICD-10 D81.3) in England, resulting in 772 bed days and 122 finished consultant episodes\(^15\).

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**
- No relevant guidance identified.

**NHS England Policies and Guidance**
CURRENT TREATMENT OPTIONS

Patients with ADA-SCID are initially treated with antibiotics, antiviral and antifungal medicines; intravenous immunoglobulins (IVIg); and prophylaxis for *Pneumocystis jiroveci*; but most ultimately require a stem cell transplant. Untreated patients with ADA-SCID that present in infancy usually die within the first two years of life. The recommended treatment is based on allogeneic haematological stem cell transplantation (HSCT) from an HLA identical healthy sibling or close relative. HSCT is a potentially curative treatment for ADA-SCID, but the effectiveness of this treatment is dependent on the degree of HLA matching between the donor and recipient, with matched sibling or family donors providing overall survival of 86% and 81% respectively. Most patients lack an identical donor and these patients may receive HSCT from an unrelated donor, however these transplants are associated with lower survival (from 29-67% over a median of 6.5 years).

Other treatment options currently include:

1) Enzyme replacement therapy with pegylated ADA (PEG-ADA) enzyme (not licensed for use in the EU).
2) Ex-vivo autologous retroviral gene therapy (available in Milan, Italy).

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01852071, IND 15440, U01AI100801, 2P01HL073104, 0910-1006; autologous transplant of EFS-ADA modified bone marrow cells; phase II.</th>
<th>NCT01380990, 10-MI-29; lentiviral gene therapy; phase II.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Donald B. Kohn, M.D.</td>
<td>Great Ormond Street Hospital for Children.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
<td>Ongoing.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
<td>Trial registry, manufacturer.</td>
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<tr>
<td>Location</td>
<td>USA.</td>
<td>UK.</td>
</tr>
<tr>
<td>Design</td>
<td>Non-randomised, uncontrolled.</td>
<td>Non-randomised, uncontrolled.</td>
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<tr>
<td>Participants</td>
<td>n=20; ≥1 month of age; ADA-deficient SCID; ineligible for matched sibling allogeneic bone marrow transplantation.</td>
<td>n=10; ≥1 month-5 years of age; male; ADA-deficient SCID; ineligible for matched sibling allogeneic bone marrow transplantation.</td>
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<tr>
<td>Schedule</td>
<td>Autologous CD34&lt;sup&gt;+&lt;/sup&gt; cells harvested and transduced with EFS lentiviral vector encoding human ADA. Following preconditioning with busulfan, patients given treated cells by single IV infusion. Patients continue PEG-ADA enzyme replacement therapy for 1 mth after treatment.</td>
<td>Autologous CD34&lt;sup&gt;+&lt;/sup&gt; cells harvested and transduced with EFS lentiviral vector encoding human ADA. Following preconditioning with busulfan, patients given 1-15 x 10&lt;sup&gt;6&lt;/sup&gt; cells/kg by single IV infusion. Patients continue PEG-ADA enzyme replacement therapy for 1 mth after treatment.</td>
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<td>Follow-up</td>
<td>Active treatment for 21-28 days, follow-up 2 yrs.</td>
<td>Active treatment for 21-28 days, follow-up 3 yrs.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Overall survival (OS); adverse events; presence of replication competent lentivirus by PCR to VSV-G gene; monoclonal expansion of blood cells by nrLAM-PCR; event-free survival as measured by number of patients alive with immune reconstitution, without allogeneic hematopoietic stem cell transplant or re-institution of enzyme replacement therapy.</td>
<td>OS.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Quantification of EFS-ADA cDNA, ADA enzyme activity, adenine nucleotides, lymphocytes, immunoglobulins and antibody response; T lymphocyte reconstitution.</td>
<td>Reduction in frequency of infections, long term immune reconstitution as assessed by sustained improvement in thymic function.</td>
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<td>Expected reporting date</td>
<td>Anticipated study completion Q4 2018.</td>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of EFS-ADA lentiviral gene therapy is not yet known.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: reduced need for regular clinic attendance for IV treatment.
- No impact identified

**Impact on Health and Social Care Services**

- Increased use of existing services
- Decreased use of existing services: reduced need for regular clinic attendance for IV treatment, follow-up and management of complications.
- Re-organisation of existing services
- Need for new services
- Other:
- None identified
Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Other increase in costs: new licensed treatment.
- Reduced drug treatment costs
- Other reduction in costs: may be reduction in ongoing need for treatment, follow up and management of complications.
- Other:
  - None identified

Other Issues

- Clinical uncertainty or other research question identified:
  - None identified

REFERENCES