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HEALTH TECHNOLOGY BRIEFING AUGUST 2020

OTL-103 for Wiskott-Aldrich syndrome

NIHRIO ID	7993	**NICE ID**	10293
Developer/Company	Orchard Therapeutics (Europe) Limited	**UKPS ID**	655587

Licensing and market availability plans	Currently in phase III clinical trial.

SUMMARY

OTL-103 is in clinical development for the treatment of Wiskott-Aldrich syndrome (WAS). WAS is a rare disease with immunological deficiency and reduced ability to form blood clots. This syndrome is caused by an abnormality in the gene found on the X chromosome that codes for WAS protein (WASP). This WAS gene defect and the severity of the condition varies widely between individuals. Severe cases may be present soon after birth or develop in the first year of life. WAS affects the functions of white blood cells and platelets, making people affected susceptible to serious infections and bleeding events. WAS occur almost exclusively in males. It is life-threatening and long-term debilitating disease due to recurrent infections that can lead to sepsis, bleeding episodes and cancer. Stem cell transplantation is the only treatment currently available to stabilize WAS.

OTL-103 is administered intravenously. It is made up of immature bone marrow cells (called $CD34^+$ cells) taken from the patient. It works by correcting cells using a modified virus that contains the correct gene for the WAS protein. When these corrected cells are transplanted back into the patient, they populate the bone marrow and produce healthy platelets and immune cells that produce the WAS protein, thereby relieving the symptoms of the disease. If licensed, OTL-103 will provide a treatment option for patients with WAS.

PROPOSED INDICATION

Treatment of Wiskott-Aldrich Syndrome (WAS).[a,1,2]

TECHNOLOGY

DESCRIPTION

OTL-103 (previously GSK2696275) is a gene therapy that consists of autologous $CD34^+$ haematopoietic stem and progenitor cells transduced with a lentiviral vector encoding human WASP.[1] When administered to a patient following the administration of a reduced-intensity conditioning regimen, the WAS gene included with the lentiviral vector is expressed in vivo in a physiological manner. This ameliorates the morbidity associated with dysfunctional WASP expression.[3,4]

OTL-103 is currently in clinical development for the treatment of WAS. In the phase III and phase I/II clinical trial (NCT03837483; NCT01515462), patients received intravenous infusion of genetically modified autologous $CD34^+$ cell enriched population that contains haematopoietic stem and progenitor cells (HSPC) transduced ex vivo with a lentiviral vector encoding the human WAS gene.[a,1,2]

INNOVATION AND/OR ADVANTAGES

To date the only definitive treatment is haematopoietic stem cell transplantation (HSCT).[5] Stem transplantation from a human leukocyte antigen (HLA)-identical donor is the treatment of choice for patients with WAS, but such a donor is not always available. In addition, patients can be hampered by development of graft-versus-host disease, graft rejection, or autoimmune complications if complete chimerism is not achieved. OTL-103 treatment does not require a donor and has decreased toxicity due to reduced intensity conditioning regimen.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

OTL-103 does not currently have Marketing Authorisation in the EU/UK for any indication.

In 2012, OTL-103 was granted orphan designation in the EU for the treatment of Wiskott-Aldrich syndrome.[6]

PATIENT GROUP

DISEASE BACKGROUND

WAS is a rare, genetically-transmitted systemic immune deficiency and platelet disorder resulting from a defect in a protein called WASP and manifesting clinically in severe recurrent infections, easy bruising and bleeding, autoimmunity and cancers. The severity of disease can range from mild to severe, even in patients with the identical WAS mutation.[7] WAS-related disorders are X-linked recessive genetic diseases that occur almost exclusively in males. X-linked recessive genetic disorders are conditions caused by an abnormal gene on the X chromosome. WAS-related disorders are caused by a mutation in the WAS gene on the X chromosome. WASP is important in the structure and function of most blood cells.[8]

[a] Information provided by Orchard Therapeutics (Europe) Limited on UK PharmaScan

The common signs and symptoms of WAS include frequent severe infections, decreased number and size of platelets (micro-thrombocytopenia), bleeding inside the brain, mucosal bleeding, bloody diarrhoea, bruising or purplish area on the skin, purpura, pinpoint red spots on the skin, life-threatening bleeding, red patches of red and irritated skin (eczema), and other skin diseases (impetigo, cellulitis and abscesses), cytomegalovirus, herpes simplex virus, Epstein-Barr virus, developing immune disorders, immune thrombocytopenic purpura, arthritis and vasculitis.[9]

People with WAS have an increased risk of developing cancer. This can be lymphomas (cancers of the lymph nodes) and leukaemias (cancers of the blood). Your doctors will check and monitor this carefully.[10]

CLINICAL NEED AND BURDEN OF DISEASE

The incidence of WAS has been estimated at less than 1 in 100,000 live births.[5] WAS affects approximately 0.01 in 10,000 people in the European Union.[6]

The Hospital Episode Statistics for England 2018/19 recorded 626 finished consultant episodes (FCE), 534 hospital admissions, 2343 FCE bed days and 384 day cases for immunodeficiency associated with other major defects (ICD 10 code D82).[11]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

WAS is complex multisystem disorder, in which patients can rapidly deteriorate in an unpredictable manner. Patients are best managed by a multidisciplinary team experienced in managing WAS patients including paediatric immunologists, stem cell transplant physicians, dermatologists, gastroenterologists, clinical geneticists, dieticians, occupational therapists, development clinicians and social support teams.[12]

Treatment involves supportive therapy preventing infection, management of thrombocytopenia, autoimmune and autoinflammatory symptoms. Stem cell transplantation, such as a bone marrow transplant, is the only treatment currently indicated to stabilize WAS and the treatment of choice for those with severe clinical symptoms. Gene therapy is also being developed as a potential therapeutic option.[10]

CURRENT TREATMENT OPTIONS

Currently, there are no NICE recommended pharmacological treatment options for WAS.

PLACE OF TECHNOLOGY

If licensed, OTL-103 will provide a treatment option for patients with WAS.

CLINICAL TRIAL INFORMATION

Trial	NCT03837483, EudraCT 2018-003842-18; a single arm, open-label clinical trial of hematopoietic stem cell gene therapy with cryopreserved autologous $CD34^+$ cells transduced with lentiviral vector encoding WAS cDNA in subjects with Wiskott-Aldrich syndrome (**WAS**) **Trial phase III** – Active, not recruiting **Location(s):** Italy **Primary completion date:** February 2022
Trial design	Single group assignment, open label
Population	N= 6; aged up to 65 years; diagnosis of WAS; no HLA-identical related donor for HSCT
Intervention(s)	OTL-103, Autologous $CD34^+$ hematopoietic stem and progenitor cells transduced *ex vivo* with a lentiviral vector encoding the human WAS gene
Comparator(s)	No comparator
Outcome(s)	Number of participants with successful engraftment of OTL-103 (Time frame: 6 months) See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**201228;** NCT01515462, EudraCT2009-017346-32**;** This will be a single-arm study. All subjects will receive OTL-103 gene therapy and will be followed up for 8 years post gene therapy **Trial phase I/II** – Active, not recruiting **Location(s):** Italy **Primary completion date:** September 2020[c]
Trial design	Single group assignment, open label
Population	N= 8, child, adults or older adults; diagnosis of WAS, no HLA-identical sibling donor, negative search for a matched unrelated donor (10/10) or an adequate unrelated cord blood donor (5-6/6) within 4-6 months
Intervention(s)	OTL-103 gene therapy Intravenous (IV) infusion of OTL-103 gene therapy. Subjects affected by *WAS* who don't have a suitable matched donor for allogenic hematopoietic stem cell transplantation will be included
Comparator(s)	No comparator
Outcome(s)	• Conditioning regimen-related safety (Time frame: Two months after gene therapy)

	• Safety of lentivirus gene transfer into HSC (Time frame: 3 years) • Sustained engraftment of genetically corrected haematopoietic stem cells in peripheral blood and/or in bone marrow (Time frame: 1 year) • Expression of vector-derived WASP (Time frame: 1 year) • Improved T-cell functions (Time frame: 3 years) • Antigen-specific responses to vaccination (Time frame: >1year) • Improved platelet count and MPV normalization (Time frame: 3 years) • Overall survival (Time frame: 3 years) See trial record for full list of other outcomes
Results (efficacy)	At the time of the interim analysis (data cut-off 29 April 2016), median follow-up was 3·6 years (range 0·5 - 5·6). Overall survival was 100%. Engraftment of genetically corrected HSPCs was successful and sustained in all patients. The fraction of WASP-positive lymphocytes increased from a median of 3·9% (range 1·8-35·6) before gene therapy to 66·7% (55·7-98·6) at 12 months after gene therapy, whereas WASP-positive platelets increased from 19·1% (range 4·1-31·0) to 76·6% (53·1-98·4). Improvement of immune function was shown by normalisation of in-vitro T-cell function and successful discontinuation of immunoglobulin supplementation in seven patients with follow-up longer than 1 year, followed by positive antigen-specific response to vaccination. Severe infections fell from 2·38 (95% CI 1·44-3·72) per patient-year of observation (PYO) in the year before gene therapy to 0·31 (0·04-1·11) per PYO in the second year after gene therapy and 0·17 (0·00-0·93) per PYO in the third year after gene therapy. At the last follow-up visit, the platelet count had increased to 20-50 × 10^9 per L in one patient, 50-100 × 10^9 per L in five patients, and more than 100 × 10^9 per L in two patients, which resulted in independence from platelet transfusions and absence of severe bleeding events.[4]
Results (safety)	27 serious adverse events in six patients occurred after gene therapy, 23 (85%) of which were infectious (pyrexia [five events in three patients], device-related infections, including one case of sepsis [four events in three patients], and gastroenteritis, including one case due to rotavirus [three events in two patients]); these occurred mainly in the first 6 months of follow-up. No adverse reactions to the investigational drug product and no abnormal clonal proliferation or leukaemia were reported after gene therapy.[4]

ESTIMATED COST

The estimated cost of OTL-103 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified

OTHER GUIDANCE

- Wiskott-Aldrich syndrome: diagnosis, current, management, and emerging treatment. 2014.[13]

ADDITIONAL INFORMATION

REFERENCES

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