NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
February 2023

Ravulizumab for treating Thrombotic Microangiopathies following Haematopoietic Stem Cell Transplantation in Children

Company/Developer	Alexion Pharmaceuticals Inc

☐New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30534	NICE TSID: 10642	UKPS ID: 660230

Licensing and Market Availability Plans

Currently in phase 3 clinical development.

Summary

Ravulizumab is in development for the treatment of thrombotic microangiopathies following haematopoietic stem cell transplantation (HSCT-TMA) in children, adolescents, and adults. Thrombotic microangiopathies (TMA) are clinical syndromes defined by the destruction of red blood cells, low platelets, and organ damage due to the formation of microscopic blood clots in capillaries and small arteries. Haematopoietic stem cell transplantation (HSCT) associated thrombotic microangiopathy, can occur after a HSCT and can often be fatal. Currently there are no approved therapies for the treatment of HSCT-TMA and intervention usually involves withdrawal of triggering agent (e.g., immunosuppressive therapies) or management of triggering conditions.

Ravulizumab is type of protein (a monoclonal antibody) that blocks the immune system from targeting the patient's own cells. Ravulizumab works by binding to and inhibiting a component in the complement system called C5. It is given intravenously and has the potential to increase patient's quality of life and to decrease treatment burden due to its extended effect that enables every 8-week dosing. If licensed ravulizumab would be the first approved pharmacological treatment option for children and adolescents with HSCT-TMA.

Proposed Indication

Hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA) in Children.[1]

Technology

Description

Ravulizumab (Ultomiris), is a monoclonal antibody $IgG_{2/4K}$ that specifically binds to the complement protein C5, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the membrane attack complex [MAC or C5b-9]) and preventing the generation of the C5b-9. Ravulizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.[2]

Ravulizumab is currently in phase 3 development for the treatment of HSCT-TMA in adults and children (NCT04557735 and NCT04543591). Weight-based doses of Ravulizumab will be administered intravenously (IV) as a loading dose regimen followed by maintenance dosing every 4 to 8 weeks, depending on weight, for 26 weeks. The participants will also receive best supportive care.[1,3]

Key Innovation

Ravulizumab is a recombinant monoclonal antibody that inhibits terminal complement activation at the C5 protein, thereby reducing haemolysis and thrombotic microangiopathy.[4] Emerging evidence suggests that the complement system plays a key role in the pathogenesis of HSCT-TMA.[5] If approved, ravulizumab would represent the first pharmacological therapy approved for the treatment of HSCT-TMA in adult and paediatric patients.

Regulatory & Development Status

Ravulizumab currently has Marketing Authorisation in the UK for the treatment of:[2]

- Adults and paediatric patients with a body weight of 10kg or above with paroxysmal nocturnal haemoglobinuria (PNH) in patients with haemolysis with clinical symptom(s) indicative of high disease activity or in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months
- Patients with a body weight of 10kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least three months and have evidence of response to eculizumab
- As an add-on to standard therapy for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive

Ravulizumab is currently in phase 2/3 development for the following indications:[6]

- Myasthenia Gravis
- Paroxysmal nocturnal haemoglobinuria (PNH)
- Covid-19
- Atypical Haemolytic Uremic Syndrome (aHUS)
- Neuromyelitis optical spectrum disorder (NMOSD)
- Dermatomyositis
- Immunoglobulin A Nephropathy

Patient Group

Disease Area and Clinical Need

Hematopoietic stem cell transplantation-associated thrombotic microangiopathy (HSCT-TMA) is a common complication occurring post-HSCT and is associated with substantial morbidity and mortality if not promptly identified and treated. Thrombotic microangiopathy (TMA) is defined as a histopathologic lesion associated with endothelial damage and dysfunction, which leads to thrombosis of venules and arterioles. Emerging evidence suggests a central role for the complement system in the pathogenesis of HSCT-TMA. The complement system has also been shown to interact with other pathways and processes including coagulation and inflammation, all of which are activated following HSCT. Three endothelial cell-damaging "hits" are required for HSCT-TMA genesis: a genetic predisposition or existing damage, an endothelial cell-damaging conditioning regimen, and additional damaging insults. Symptoms include proteinuria, hypertension, severe abdominal pain, headache and hypoxaemia.[5 7]

In England, 2021-22, there were 1,677 finished consultant episodes (FCE) and 1,557 admissions for thrombotic microangiopathy (ICD-10 code M31.1), of which HSCT-TMA is a subset.[8] Recent studies have suggested that HSCT-TMA affects around 10-20% of patients following transplantation.[5] The incidence of HSCT-TMA has been estimated at 39% in paediatric and young adult patients, however, it has been shown that clinical diagnoses are not always given to HSCT-TMA patients, meaning the disease may be under-reported. Mortality rates have been reported to range from 40-84%.[9]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently do not recommend any therapies for the treatment of HSCT-TMA.

In recent years, the approach to treatment of HSCT-TMA has evolved based on increased understanding of underlying pathophysiology. Preventative measures such as avoidance of endothelial toxins, avoidance of infection, and optimisation of conditioning regimens may minimise endothelial injury. Aggressive supportive care including minimising transfusions, aggressive hypertension management, and treatment of any underlying infection are central to HSCT-TMA treatment. Additional approaches may include withdrawal of CNI/mTORi, therapeutic plasma exchange (TPE), rituximab, defibrotide, and eculizumab, although none of these are currently licensed.[9,10] Clinical trials have explored novel treatment approaches with various complement directed therapies including mannan-binding lectin-associated serine protease-2 inhibition (MASP-2) and second generation anti-C5 directed therapy. Prompt recognition and early initiation of treatment may lead to improved outcomes.[9]

There are currently no approved pharmacological treatment options for HSCT-TMA in paediatric patients.[11]

Clinical Trial Information

Trial	NCT04557735; EudraCT2020-000761-16; A Phase 3, Open-label, Single Arm, Multicenter Study of Ravulizumab in Addition to Best Supportive Care in Pediatric Participants With Thrombotic Microangiopathy (TMA) After Hematopoietic Stem Cell Transplantation (HSCT) **Phase III:** Active, not recruiting **Locations:** 4 EU countries, UK, United States, Japan, Republic of Korea **Estimated Primary completion date:** June 2023
Trial Design	Open-label, single group assignment

Population	N=40 (estimated); between 28 days and 17 years of age; received HSCT within the past 12 months; diagnosis of TMA that persists for at least 72 hours despite initial management
Intervention(s)	Ravulizumab (Weight based doses, intravenously administered) plus best supportive care
Comparator(s)	N/A
Outcome(s)	**Primary outcome measures:** • Proportion of participants with TMA response [Time frame: 26 weeks (treatment period)] See full trial records for full lists of outcomes.
Results (efficacy)	-
Results (safety)	-
Clinical Trial Information	
Trial	NCT04543591; EudraCT2020-000144-61; A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Ravulizumab in Adult and Adolescent Participants Who Have Thrombotic Microangiopathy (TMA) After Hematopoietic Stem Cell Transplant (HSCT) **Phase III:** Recruiting **Locations:** 9 EU countries, UK, United States, Canada and other countries **Estimated Primary completion date:** August 2023
Trial Design	Randomised, double-blind, placebo-controlled, parallel assignment
Population	N=184 (estimated); 12 years of age or older; received HSCT within the past 12 months; diagnosis of TMA that persists for at least 72 hours despite initial management
Intervention(s)	Ravulizumab IV (Weight based doses) plus best supportive care
Comparator(s)	Matching placebo plus best supportive care
Outcome(s)	Primary outcome measures: • Proportion of participants with TMA response [Time frame: 26 weeks (treatment period)] See full trial records for full lists of outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Ravulizumab is already marketed in the UK for treatment of PNH, aHUS and gMG. An 11ml vial (100mg/ml) costs £16,621.00 and a 3ml vial (100mg/ml) costs £4,533.00.[4]

Relevant Guidance

NICE Guidance

No relevant guidance could be identified at this time.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS standard contract for haematopoietic stem cell transplantation (Children). B04/S/b.

Other Guidance

- Young JA, Pallas CR, Knovich MA. Transplant-associated thrombotic microangiopathy: theoretical considerations and a practical approach to an unrefined diagnosis. 2021. [9]
- Dvorak CC, Higham C, Shimano KA. Transplant-Associated Thrombotic Microangiopathy in Pediatric Hematopoietic Cell Transplant Recipients: A Practical Approach to Diagnose and Management. 2019. [12]
- Arnold DM, Patriquin CJ, Nazy I. Thrombotic microangiopathies: a general approach to diagnosis and management. 2017. [13]

Additional Information

References

1 Clinicaltrials.gov. *Study of Ravulizumab in Pediatric Participants With HSCT-TMA*. *Trial ID: NCT04557735*. 2020. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04557735 [Accessed 20 December 2022].

2 Electronic Medicines Compendium (EMC). *Ultomiris 1,100 mg/11 mL concentrate for solution for infusion*. 2022. Available from: https://www.medicines.org.uk/emc/product/11945/smpc [Accessed 20 December 2022].

3 Clinicaltrials.gov. *Ravulizumab in Thrombotic Microangiopathy After Hematopoietic Stem Cell Transplant*. *Trial ID: NCT04543591*. 2020. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04543591 [Accessed 26 January 2023].

4 British National Formulary (BNF). *Ravulizumab*. 2022. Available from: https://bnf.nice.org.uk/drugs/ravulizumab/medicinal-forms/ [Accessed 04 January 2023].

5 Meri S, Bunjes D, Cofiell R, Jodele S. The Role of Complement in HSCT-TMA: Basic Science to Clinical Practice. *Advances in Therapy*. 2022;39(9):3896-915. Available from: https://doi.org/10.1007/s12325-022-02184-4.

6 Clinicaltrials.gov. 2022. Available from: https://clinicaltrials.gov/ct2/results?term=ravulizumab&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Accessed 20 December 2022].

7 Meri S, Bunjes D, Cofiell R, Jodele S. The Role of Complement in HSCT-TMA: Basic Science to Clinical Practice (Figure 1). *Advances in Therapy*. 2022;39(9):3896-915. Available from: https://doi.org/10.1007/s12325-022-02184-4.

8 National Health Service. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22.

9 Young JA, Pallas CR, Knovich MA. Transplant-associated thrombotic microangiopathy: theoretical considerations and a practical approach to an unrefined diagnosis. *Bone Marrow Transplantation*. 2021;56(8):1805-17. Available from: https://doi.org/10.1038/s41409-021-01283-0.

10 Kim SS, Patel M, Yum K, Keyzner A. Hematopoietic stem cell transplant-associated thrombotic microangiopathy: review of pharmacologic treatment options. *Transfusion*. 2015;55(2):452-8. Available from: https://doi.org/10.1111/trf.12859.

11 National Institute for Health and Care Excellence. 2022. Available from: https://www.nice.org.uk/search?q=transplant+associated+thrombotic+microangiopathy [Accessed 04 January 2023].

12 Dvorak CC, Higham C, Shimano KA. Transplant-Associated Thrombotic Microangiopathy in Pediatric Hematopoietic Cell Transplant Recipients: A Practical Approach to Diagnosis and Management. *Frontiers in Pediatrics*. 2019;7. Available from: https://doi.org/10.3389/fped.2019.00133.

13 Arnold DM, Patriquin CJ, Nazy I. Thrombotic microangiopathies: a general approach to diagnosis and management. *Cmaj*. 2017;189(4):E153-e9. Available from: https://doi.org/10.1503/cmaj.160142.

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