

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Rivogenlecleucel for treating haematological non-malignant diseases in children and young people undergoing haploidentical haematopoietic stem cell transplant

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of rivogenlecleucel within its marketing authorisation for treating haematological non-malignant diseases in children and young people undergoing haploidentical haematopoietic stem cell transplant.

Background

Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for children with various non-malignant diseases such as inborn errors of metabolism (metabolic disorders), primary immunodeficiencies, haemoglobinopathies (such as sickle cell disease) and bone marrow failure syndromes. An allogeneic HSCT involves replacing the bone marrow stem cells of a patient with stem cells from a tissue-type matched or mismatched donor. For many people who require allogeneic HSCT, it is often difficult to find a fully matched donor. A haploidentical donor is a donor which is a half match for the patient. More than 90% of people needing a haematopoietic stem cell transplant have a haploidentical family member. Other advantages of haploidentical haematopoietic stem cell transplant include: immediate donor availability; access for all regardless of ethnicity; the ability to select the best donor on the basis of age, sex, and infectious disease status; and access to repeated donation in case of transplant failure.

[Registry data from the British Society of Blood and Marrow Transplantation](#) (BSBMT) shows that in 2015–2017 there were between 23 and 40 paediatric haploidentical HSCTs per year.

After HSCT treatment it can take six to twelve months blood cell levels and immune cell functions to become near-normal. During this time there is a high rate of transplant rejection, graft versus host disease (GvHD), when donated white T-cells attack the body's own cells, and also to disease relapse and transplant-related mortality.

The current UK approach to approach to haploidentical HSCT is to provide patients with a T-lymphocyte replete transplant, followed by treatment with prophylactic cyclophosphamide to destroy any activated T-lymphocytes that may cause GvHD.

Draft scope for the proposed appraisal of rivogenlecleucel for treating haematological non-malignant diseases in children and young people undergoing haploidentical haematopoietic stem cell transplant. Issue Date: March 2019.

NHS England clinical commissioning policy includes combination therapy of topical therapies, calcineurin inhibitors, systemic corticosteroids, sirolimus and/or mycophenolate mofetil as options for first line treatment of acute GvHD. Extracorporeal photopheresis (ECP) is routinely commissioned as a second-line option.

NHS England clinical commissioning policy includes combination therapy of systemic corticosteroids, calcineurin inhibitors and/or sirolimus as options for first line treatment of chronic GvHD. ECP, pentostatin, rituximab and imatinib are routinely commissioned as second-line options, depending on the specific indication.

The technology

Rivogenlecleucel (Rivo-cel, Bellicum) is a genetically modified donor T-cell product. Donor T-lymphocytes are modified with a retroviral vector (BPZ-1001) and engineered to express the iCasp9 protein, which acts a “safety-switch” in the event of graft versus host disease. It is administered to patients who have received a haploidentical HSCT from the same donor as the donor of the cells in rivogenlecleucel. It is administered intravenously after initial haploidentical allogeneic HSCT.

Rimiducid (brand name unknown, Bellicum) is a dimerization (linking) agent. It activates the ICasp9 protein in rivogenlecleucel in the event of GvHD. Activation of this protein triggers programmed cell death, and the removal of rivogenlecleucel cells, which can resolve the symptoms of GvHD. It is administered intravenously.

Rivogenlecleucel and rimiducid do not currently have marketing authorisations for the treatment of haematological non-malignant disease in children and young people undergoing a haploidentical HSCT. They have been studied in single arm clinical trials in children and young people (older than 1 month and younger than 18 years old) who have non-malignant diseases and have undergone haploidentical HSCT. People received rimiducid if they developed grade III and IV GvHD following treatment with haploidentical HSCT and rivogenlecleucel. The clinical trial protocols specified that patients were eligible for treatment with rimiducid if the GvHD had an inadequate response to steroids within 48 hours of treatment or was mild to severe chronic GvHD with inadequate response to steroids within 7 days of treatment.

The trials also evaluate rivogenlecleucel as a treatment of haematological cancers in children and young people and have undergone haploidentical HSCT. This population will be considered in a separate NICE technology appraisal of rivogenlecleucel.

Intervention(s)	Rivogenlecleucel as an adjunct to haploidentical haematopoietic stem cell transplant
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Population(s)	Children and young people with haematological non-malignant diseases (including but not limited to metabolic disorders, primary immunodeficiencies, haemoglobinopathies [such as sickle cell disease] and bone marrow failure syndromes) undergoing haploidentical haematopoietic stem cell transplant
Comparators	Established clinical management for haploidentical haematopoietic stem cell transplant without rivogenlecleucel
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • mortality • relapse of underlying condition • success of stem cell transplantation (engraftment) • immune system recovery • time to and incidence of infections • time to and incidence of <ul style="list-style-type: none"> ○ acute GvHD ○ chronic GvHD • response to treatment for GvHD • adverse effects of treatment • health-related quality of life.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The costs and benefits of treatments for graft versus host disease (rimiducid or established clinical management) should be considered in the modelling.</p> <p>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.</p>

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 and NICE Pathways	Related Technology Appraisals: None
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) : Chapter 29. Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1 to 4. NHS England (2017) Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages) NHS England (2015) Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised

Questions for consultation

Would rivogenlecleucel be considered for all non-malignant diseases in children and young people where haploidentical HSCT is an appropriate intervention?

Is it appropriate to conduct separate appraisals of rivogenlecleucel for haematological cancers and non-malignant diseases?

Which treatments are considered to be established clinical practice in the NHS for children and young people with non-malignant disease undergoing haploidentical HSCT? Is standard care consistent across:

- diseases,
- age groups?

Would rivogenlecleucel be used in addition to current standard care for treating immunodeficiency following haploidentical HSCT?

Which prophylactic treatments (if any) would be used to minimise the risk of graft versus host disease in children and young people with non-malignant disease undergoing haploidentical HSCT?

- Would rivogenlecleucel be used in addition to prophylactic treatment for GvHD or as an alternative to prophylactic treatment?

Which treatments are considered to be established clinical practice in the NHS in England for GvHD? Is established clinical management consistent across:

- diseases,
- age groups,

Would rimiducid be used in addition to established clinical management for GvHD which is refractory to corticosteroids?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom rivogenlecleucel is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which rivogenlecleucel will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider rivogenlecleucel to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of rivogenlecleucel can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>).

References

- 1) British Society of Blood and Marrow Transplantation Registry (2015 to 2017 activity): <http://bsbmt.org/> (accessed February 2018)