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HEALTH TECHNOLOGY BRIEFING JANUARY 2021

Inolimomab for acute Graft versus Host Disease

NIHRIO ID	29560	NICE ID	10516
Developer/Company	ElsaLys Biotech	UKPS ID	N/A

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

SUMMARY

Inolimomab is being developed for the treatment of grade II to IV steroid-refractory acute Graft versus Host Disease (aGvHD) in adult patients after allogeneic haematopoietic stem cell transplantation (aHSCT). GvHD is characterised as a frequent complication of bone marrow transplantation and involves a reaction between the donor cells and the recipient's native tissues, leading to injury of the recipient's tissues. GvHD occurs in acute and chronic form. The organs most commonly affected in aGvHD are the stomach and the intestines, the skin, and the liver. Up to 50% of aGvHD patients do not respond to initial steroid treatment and are left with few therapeutic options.

Inolimomab, administered intravenously, is an artificially produced antibody that specifically recognises a protein, the CD25 antibody, found on those cells of the immune system that are activated, thereby causing the GvHD. Inolimomab is expected to bind to these cells and stop their multiplication. Cells which are not involved in the GvHD immune reaction and, therefore, not activated at the time of the administration of the product, would be preserved. If licensed, inolimomab would offer an additional treatment option for adult patients with grade II to IV steroid-refractory aGvHD after aHSCT.

PROPOSED INDICATION

Adult patients aged 18 years and over, with grade II to IV steroid-refractory acute Graft versus Host Disease (aGvHD) after allogeneic haematopoietic stem cell transplant (aHSCT).[1,2]

TECHNOLOGY

DESCRIPTION

Inolimomab (LEUKOTAC) is an immunotherapy monoclonal antibody that targets the interleukin-2 receptor (IL-2), a chemical molecule named cytokine that contributes to the development and proliferation of some white blood cells including T-cells responsible for aGvHD. By linking specifically to the α chain of the receptor (CD25), inolimomab prevents IL-2 from binding on the surface of the donor's over-active T-cells which blocks their multiplication.[3]

In the phase III clinical trial (Eudra CT 2007-005009-24) patients were administered 0.3 mg/kg of inolimomab intravenously (IV) per day for the induction phase and 0.2 mg/kg per day for maintenance phase (days 9-.[1,4]

INNOVATION AND/OR ADVANTAGES

Despite prophylaxis with immunosuppressive therapy agents, nearly 50% of patients have acute Graft versus Host Disease (aGvHD) after allogeneic hematopoietic cell transplantation.[4] Even though immunosuppressive therapies may achieve a response, unsatisfactory aGVHD control and toxicity of high cumulative doses of corticosteroids are frequent, notably with an increased infection rate.[5] Therefore, as the number of patients undergoing aHSCT increases, developing safe and effective treatments for aGvHD will become increasingly important, especially for those whose disease becomes refractory to systemic steroid therapy.[6]

Inolimomab has been associated with encouraging response and short-term survival rates in the setting of steroid-refractory aGvHD.[4] Results from a retrospective study showed that inolimomab was well-tolerated and effective for severe steroid-resistant aGvHD where the use of the murine monoclonal antibody inolimomab resulted in a total response rate of 63% among 85 patients with no side effects.[7] Results from another study suggests that inolimomab may be an effective salvage therapy for patients with steroid-refractory aGVHD.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Inolimomab is does not currently have Marketing Authorisation in the EU/UK for any indication.

Inolimomab is also currently in a phase III clinical development for the treatment of steroid-refractory GvHD in paediatric patients.[9]

Inolimomab was granted an orphan drug designation in the EU by the EMA in March 2001 and in the US by the US FDA in October 2002 for the treatment of GvHD.[10,11]

PATIENT GROUP

DISEASE BACKGROUND

GvHD is a common complication of aHSCT and major cause of post-transplant mortality and morbidity. It is caused by immune incompatibility between the graft (donor) and recipient tissues. The graft cells recognise the recipient tissues as foreign and mount an immune response against them. GvHD can affect the skin, mouth, eyes, lung, liver and gut. There are two types of GvHD: acute and chronic. Acute (aGvHD) generally starts within 100 days of transplant, with chronic GvHD (cGvHD) 100 days after it.[12]

aGvHD may occur in aHSCT recipients despite prophylaxis. The incidence and severity of aGvHD depend on a variety of risk factors, but it occurs more frequently with increased severity after aHSCT from human leukocyte antigen (HLA)-nonidentical or unrelated donors than from HLA-matched sibling donors. Non-HLA risk factors associated with aGvHD include:[6,13]

- older patient and/or donor age,
- use of female donor for male recipient,
- use of peripheral blood as stem cell source,
- nature of GVHD prophylaxis,
- recipient seropositivity for cytomegalovirus, and
- total body irradiation.

aGvHD is characterised by a generalised patchy skin rash, sickness, weight loss, loss of appetite, watery diarrhoea, severe abdominal pain, bloody diarrhoea, and jaundice. aGvHD is graded in severity from I (mild) through II (moderate), III (severe) to IV (very severe) according to the modified Seattle Glucksberg criteria.[12]

CLINICAL NEED AND BURDEN OF DISEASE

GvHD was considered to affect approximately 0.13 in 10,000 persons in the European Union in 2008.[10] aGvHD develops in 30%-55% of patients receiving aHSCT, and high dose corticosteroid treatment can be initiated in patients with grade ≥II aGvHD.[14,15] However, up to 50% of patients fail to obtain a satisfactory response with steroid treatment alone.[15] aGvHD is the major cause of morbidity and mortality in this setting with those who fail initial steroid therapy have mortality rates as high as 95%.[14,16] The survival prognosis of aGvHD correlates to the grade of disease severity with 5-year survival of 25% for grade III and 5% for grade IV disease.[12]

In 2019, the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) reported a total of all peripheral stem cell transplants (SCTs) in UK and Republic of Ireland to be 1,400.[17] The hospital episode statistics (HES) for procedures or interventions for England in 2019-2020, recorded a total of 1,130 finished consultant episodes for allogeneic peripheral blood stem cell transplant (OPCS4 X33.6).[18]

Using the BSBMTCT 2019 data and applying the estimate of 30-55% for aGvHD developing in HSCT patients of which 50% of patients will develop steroid-resistant aGvHD, between 420 to 770 patients could develop aGvHD of which between 210 to 385 patients could benefit from inolimomab treatment.[14,15,17]

Using the HES procedures and intervention data from 2019-20 and applying the estimate of 30-55% for aGvHD developing in HSCT patients of which 50% of patients will develop steroid-resistant aGvHD, between 339 to 621 patients could develop aGvHD of which between 169 to 310 patients could benefit from inolimomab treatment.[14,15,18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

A multidisciplinary team is called with the accountable transplant physician, nurse and consultant in whichever organ is principally involved to discuss treatment options available. In the case of aGvHD, the accountable transplant physician is responsible for continuous oversight of treatment. The goal of any treatment is the effective control of GvHD whilst minimising the risk of toxicity and relapse. In many cases, patients are treated prophylactically where high probability of GvHD is present.[12]

Depending on the type of GvHD, the following treatments may be considered by clinicians to treat their patients:[12]

- other medicines that reduce the body's immune response (immunosuppressants)
- a therapy where white blood cells are exposed to UVA light (called 'extracorporeal photopheresis' or ECP)
- an infusion of specially prepared stem cells (called 'mesenchymal' stem cells).

Clinically, treatment of GvHD is highly individualised, based upon clinical response. First line treatments include topical therapies, systemic corticosteroids or calcineurin inhibitors. Second line or subsequent therapy is guided by grade and clinical presentation of GvHD and treatments of clinical interest include other immunosuppressant therapies such as imatinib and sirolimus, newer biological therapies such as rituximab and infliximab and ECP, and cell therapy such as mesenchymal stem cells.[12]

CURRENT TREATMENT OPTIONS

According to NHS England, the following treatment options are recommended for steroid-refractory aGvHD following aHSCT:[12]

- extracorporeal photopheresis (ECP)
- combination therapy with the following treatments indicated: mammalian target of rapamycin inhibitors (sirolimus) and/or mycophenolate mofetil.

PLACE OF TECHNOLOGY

If licensed, inolimomab would offer an additional treatment option for adult patients with grade II to IV steroid-refractory aGvHD after aHSCT.

CLINICAL TRIAL INFORMATION

Trial	Eudra CT 2007-005009-24; An international randomised, multicentre, parallel-group, Phase III comparative study of inolimomab against usual care in the Treatment of Primary Steroid Refractory Acute Graft versus Host Disease (aGvHD) following allogeneic Stem Cell Transplantation in adult patients. **Phase III –** Completed **Location(s):** France and Belgium
Trial design	Randomised, parallel-assignment, open-label

Population	N=100 (planned); adult patients with primary steroid-resistant aGvHD following allogeneic stem cell transplantation for haematological malignancies; aged 18 years and over
Intervention(s)	0.3 mg/kg of inolimomab administered IV per day for the induction phase and 0.2 mg/kg per day for maintenance[4]
Comparator(s)	2.5 mg/kg of antithymocyte globulin (ATG) for 4 consecutive days[4]
Outcome(s)	Primary outcome: Therapy success defined as overall survival at one year without replacement of the baseline allocated treatment See trial record for full list of all outcomes
Results (efficacy)	The primary end point of this randomized phase 3 trial was not achieved. In steroid-resistant aGVHD 1-year survival without changing baseline therapy was not different after inolimomab vs ATG: [4] • 14 patients (28.5%) in the inolimomab vs. 11 patients (21.5%) in the ATG arms, with a hazard ratio of 0.874 (P = 0.28) • With a minimum follow-up of 1 year, 26 (53%) and 31 (60%) patients died in the inolimomab and ATG arms, respectively.
Results (safety)	Adverse events were similar in the 2 arms, with fewer viral infections in the inolimomab arm compared with the ATG arm.[4]

Trial	Eudra CT 2006-005019-81; A European Open-Label, Multicentre, Phase II Study of Inolimomab in the Treatment of Primary Steroid Resistant Acute Graft versus Host Disease (aGvHD) following allogeneic Stem Cell Transplantation for Hematological Malignancies in Adult patients **Phase II –** Ongoing **Location(s):** France
Trial design	Non-randomised, open-label
Population	N=40 (planned); adult patients with primary steroid-resistant aGvHD following allogeneic stem cell transplantation for hematological malignancies (aSCT); aged 18 years and over
Intervention(s)	1 mg/ml of inolimomab administered intravenously
Comparator(s)	No comparator
Outcome(s)	Primary outcome: Overall Response Rate (CR + PR) at D29 after initiation of Inolimomab in patients with primary steroid-resistant aGvHD after aSCT See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of inolimomab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation. NHS England: 16069/P. March 2017.

OTHER GUIDANCE

- British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation (BCSH/BSBMT). Diagnosis and management of acute graft-versus-host disease. 2012.[19]
- American Society of Blood and Marrow Transplantation (ASBMT). First- and Second-Line Systemic Treatment of Acute Graft-versus-Host Disease: Recommendations of the American Society of Blood and Marrow Transplantation. 2012.[20]

ADDITIONAL INFORMATION

ElsaLys Biotech did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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