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Health Technology Briefing
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Abatacept with a calcineurin inhibitor and methotrexate for prophylaxis of acute graft versus host disease

Company/Developer	Bristol-Myers Squibb Pharmaceuticals

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30006	NICE ID: 10679	UKPS ID: 661441

Licensing and Market Availability Plans

Currently in phase II clinical trials

Summary

Abatacept, in combination with standard prophylaxis treatments, is being developed for the prophylaxis of acute graft versus host disease (aGvHD) in unrelated-donor hematopoietic stem cell transplantation (HSCT). 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 affected in aGvHD are the stomach, intestines, skin, and liver. Between 30-55% of patients with a HSCT go on to develop aGvHD and with no approved prophylaxis treatment options, there is significant unmet need.

Abatacept is a disease modifying drug that disrupts T-cell regulation by binding to CD80 and CD86, which are proteins found on antigen presenting cells. The binding of antigen presenting cells to T cells is key for T cell activation. By preventing the activation of these immune cells, they cannot attack and kill the transplanted cells which would cause damage to tissues and increase the risk of transplantation failure. If licensed, abatacept will offer a prophylaxis treatment option for the prevention of aGvHD in patients over 6 years of age.

Proposed Indication

Patients 6 years of age and older for the prophylaxis of acute graft versus disease (aGvHD) in unrelated-donor hematopoietic stem cell transplantation (HSCT).[1]

Technology

Description

Abatacept (Orencia) is a fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to a modified Fc portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in Chinese hamster ovary cells. Abatacept selectively modulates a key costimulatory signal required for full activation of T lymphocytes expressing CD28. Full activation of T lymphocytes requires two signals provided by antigen presenting cells: recognition of a specific antigen by a T cell receptor (signal 1) and a second, costimulatory signal. A major costimulatory pathway involves the binding of CD80 and CD86 molecules on the surface of antigen presenting cells to the CD28 receptor on T lymphocytes (signal 2). Abatacept selectively inhibits this costimulatory pathway by specifically binding to CD80 and CD86. Studies indicate that naive T lymphocyte responses are more affected by abatacept than memory T lymphocyte responses.[2] This is important in relation to GvHD as in this disease, T lymphocytes recognise donor cells as foreign and attack healthy tissues and organs. By preventing T cells binding, there is a reduction in host cell damage.[3]

In a phase II clinical trial (NCT01743131), abatacept is given, with a calcineurin inhibitor (CNI) and methotrexate (MTX) at 10mg/kg dose over 60 minutes on day -1 (the day before transplantation), followed by days 5, 14 and 28 after transplantation.[1,3]

Key Innovation

HSCTs can be a curative option for patients with several diseases. However, the myeloablative preparative treatment regimens that these patients undergo are associated with GvHD. In preclinical models, the administration of a CTLA-4 antibody such as abatacept led to the prevention of acute and chronic GvHD.[4] Therefore, if approved, abatacept may provide a better treatment option for the prevention of GvHD in patients undergoing HSCT.

If licensed, abatacept, combined with a CNI and MTX, would offer an approved option for the prophylaxis of aGvHD in patients over 6 years old.

Regulatory & Development Status

Abatacept is currently marketed in the EU/UK for the following indications:[2]

- In combination with MTX for the treatment of moderate to severe rheumatoid arthritis (RA) in adults who responded inadequately to previous disease-modifying anti-rheumatic drug (DMARD) therapy including methotrexate or a TNF alpha inhibitor
- In combination with MTX for the treatment of highly active and progressive disease in adults with RA not previously treated with MTX
- In combination with MTX to reduce the progression of joint damage and improvement of physical function
- As a monotherapy, or in combination with MTX for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy including MTX has been inadequate, and for whom additional systemic therapy for psoriatic skin lesions is not required
- In combination with MTX for treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients 6 years and older who have had an inadequate response to previous DMARD therapy

Abatacept is currently in phase III/II clinical trials for a number of indications including:[5]

- Idiopathic inflammatory myopathy
- Rheumatoid arthritis
- Psoriatic arthritis
- Systemic lupus erythematosus
- Alopecia areata
- Ulcerative colitis
- Primary sjögrens syndrome
- Psoriasis vulgaris
- Interstitial lung disease
- Uveitis
- Systemic sclerosis
- Idiopathic arthritis

Abatacept has been awarded a Breakthrough Therapy designation by the US FDA for aGvHD in April 2019.[6]

Patient Group

Disease Area and Clinical Need

GvHD is a common complication of autologous HSCT (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.[7] 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.[8] aGvHD is characterised by a generalised patchy skin rash, sickness, weight loss, loss of appetite, watery or bloody diarrhoea, severe abdominal pain, 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.[7]

GvHD was considered to affect approximately 0.13 in 10,000 persons in the European Union in 2008.[9] 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.[7] In 2019, the British Society of Blood and Marrow Transplantation and Cellular Therapy reported a total of all peripheral stem cell transplants in UK and Republic of Ireland to be 1,400.[10] The hospital episode statistics (HES) for procedures or interventions for England in 2020-2021, recorded a total of 859 finished consultant episodes for allogeneic peripheral blood stem cell transplant (OPCS4 X33.6).[11] Using the HES procedures and intervention data from 2020-21 and applying the estimate of 31-50% for aGvHD developing in HSCT patients, between 266 to 429 patients could develop aGvHD.[7,11]

Recommended Treatment Options

Current prophylaxis options for aGvHD are ciclosporin, MTX, alemtuzumab, mycophenolate mofetil and antithymocytic globulin but there are currently no approved therapies.[12]

According to NHS England, the extracorporeal photopheresis is recommended for aGvHD following aHSCT.[7]

Clinical Trial Information	
Trial	**ABA2; NCT01743131;** Abatacept Combined With a Calcineurin Inhibitor and Methotrexate for Graft Versus Host Disease Prophylaxis: A Randomized Controlled Trial **Phase II –** active, not recruiting **Location(s):** US and Canada **Primary Completion Date:** June 2018
Trial Design	Randomised, parallel assignment, triple-blinded, placebo controlled
Population	N=186; 6 years and older; have a willing unrelated adult donor
Intervention(s)	Abatacept (10mg/kg) at day -1, 5, 14 and 28 in combination with standard GVHD prophylaxis (calcineurin inhibitor (cyclosporine or tacrolimus) and MTX)[3]
Comparator(s)	Matched placebo
Outcome(s)	Percentage of participants with cumulative incidence of severe aGVHD at day +100 post-transplant [Time frame: first 100 days after transplant]
Results (efficacy)	• In the 8/8 HLA-matched cohort, an estimated rate of grade III-IV aGvHD-free survival of 87% was observed for the abatacept + CNI + MTX group versus 75% for placebo + CNI + MTX (Hazard Ratio [HR] 0.55, 95% Confidence Interval [CI]: 0.26 to 1.18) • An estimated rate of grade II-IV aGvHD-free survival of 50% was observed for the Orencia IV + CNI + MTX group versus 32% for placebo + CNI + MTX (HR 0.54, 95% CI: 0.35 to 0.83). • aGvHD-free survival was measured from the date of transplantation until the onset of documented aGvHD or death by any cause up to day 180 post-transplantation. The rate of estimated overall survival was 97% for the abatacept + CNI + MTX group versus 84% for placebo + CNI + MTX (HR 0.33, 95% CI: 0.12 to 0.93). • In an exploratory analysis of the 7/8 cohort of abatacept-treated patients (n=43), the rates of grade III-IV aGvHD-free survival, grade II-IV aGvHD-free survival, and overall survival at day 180 post-transplantation were 95% (95% CI: 83% to 99%), 53% (95% CI: 38% to 67%), and 98% (95% CI: 85% to 100%), respectively.[3,13]
Results (safety)	• Serious adverse events reported in >5% of patients who received abatacept (Orencia) in combination with a CNI and MTX included pyrexia (20%), pneumonia (8%), acute kidney injury (7%), diarrhoea (6%), hypoxia (5%), and nausea (5%). Permanent discontinuation of Orencia occurred in two patients (1.7%) due to one case each of pneumonia and allergic reaction. • The most frequent adverse events of all grades reported in ≥10% of patients with aGvHD who received abatacept with a difference of ≥2% for the 7/8 cohort, 8/8 cohort abatacept arm, and 8/8 cohort placebo arm,

	respectively, were anaemia (56%, 69%, and 57%), CD4 lymphocytes decreased (14%, 14%, and 9%), hypertension (49%, 43%, and 38%), pyrexia (28%, 19%, and 20%), CMV reactivation/CMV infection (26%, 32%, and 22%), pneumonia (19%, 12%, and 10%), epistaxis (12%, 16%, and 10%), acute kidney injury (9%, 15%, and 10%), and hypermagnesemia (5%, 18%, 10%). • Incidence rates of grade III or IV adverse events were the same as incidence rates of all grades, with the exception of grade III or IV pyrexia in all arms (9% [7/8 cohort], 10% [8/8 cohort, abatacept arm], and 4% [8/8 cohort, placebo arm]), pneumonia in the 8/8 cohort placebo arm (9%) and acute kidney injury in the 7/8 cohort abatacept arm (7%).2 Clinically relevant adverse reactions in <10% of patients who received abatacept in combination with CNI and MTX in Study GVHD-1 included Epstein-Barr Virus (EBV) reactivation.[3]

Estimated Cost

The cost of 125mg/1ml abatacept is £1209.60.[14]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Inolimomab (Leukotac) for acute Graft versus host disease (aGvHD) after Allo-HSCT (GID-TA10823). Expected date of issue to be confirmed.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation. 16069/P. March 2017.
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation. NHSCB/B04/P/a. April 2013.

Other Guidance

- Penack O, Marchetti M, Ruutu T, Aljurf M, Bacigalupo A, Bonifazi F et al. Prophylaxis and management of graft versus host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation. February 2020.[15]
- Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P et al. Diagnosis and management of acute graft-versus-host disease. April 2012.[16]

Additional Information

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