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Horizon Scanning Research & Intelligence Centre

Remestemcel-L (Prochymal) for steroid refractory acute graft versus host disease – second line

SUMMARY

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Remestemcel-L (Prochymal) is intended to be used as second line therapy for the treatment of steroid refractory acute graft versus host disease (GVHD). If licensed, it would offer a novel additional intravenous treatment option for this patient group, who currently have few effective therapies available. Remestemcel-L is a cell therapy product containing human mesenchymal stem cells that are involved in tissue repair through the coordinated release of tissue specific growth factors. Remestemcel-L does not currently have Marketing Authorisation in the EU for any indication.

It is estimated that between 20% and 80% of patients undergoing an allogeneic haematopoietic stem cell transplant will develop some form of GVHD. The incidence of acute GVHD varies widely, ranging from 10-80% depending on risk factors such as mismatched donors and older age. Morbidity and mortality rates continue to rise above 70% in steroid refractory patients with acute GVHD.

Management of GVHD is largely focused on prevention through immunosuppression of donor T-cells with immunomodulatory agents or through depletion of T-cells before or after transplant, using monoclonal or polyclonal antibodies. Generally, immunosuppression is initiated using methotrexate, followed by ciclosporin or tacrolimus post-transplant. Corticosteroid treatment is recommended in patients with acute GVHD, however this is effective in less than 50%. Remestemcel-L has completed two phase III clinical trials comparing its effect on complete response against treatment with placebo.

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TARGET GROUP

- Graft versus host disease: acute; steroid refractory; in adults – second line.

TECHNOLOGY

DESCRIPTION

Remestemcel-L (Prochymal, Provacel, Stromagen, JR-0301, MSC-100, OTI-010) is a cell therapy product containing human mesenchymal stem cells (MSC). The MSCs are non-immunogenic and have the ability to engraft and selectively differentiate, based on tissue environment, to various tissue lineages. At the cellular level, activity of MSCs leads to tissue repair through a coordinated release of tissue specific growth factors. Remestemcel-L counteracts T-cell mediated inflammatory processes through down-regulating the production of pro-inflammatory cytokines, tumour necrosis factor-α (TNF-α) and interferon gamma. Remestemcel-L is intended for the second line treatment of steroid refractory acute graft versus host disease (GVHD) in adult patients. In phase III clinical trials, remestemcel-L was administered by intravenous (IV) infusion at $2x10^6$ MSCs/kg, twice weekly for four weeks, then once weekly for two additional weeks[1,2].

Remestemcel-L does not currently have Marketing Authorisation in the EU for any indication. Remestemcel-L is currently in phase III clinical trials for Crohn's disease, newly diagnosed acute GVHD, severe and acute GVHD in paediatric patients, and for radiation poisoning. It is also in phase II clinical trials for the treatment of chronic obstructive pulmonary disease and myocardial infarction.

INNOVATION and/or ADVANTAGES

If licensed, remestemcel-L will offer a novel additional IV treatment option for adult patients with acute steroid refractory GVHD, who currently have few effective therapies available.

DEVELOPER

Mesoblast.

AVAILABILITY, LAUNCH OR MARKETING

Completed phase III clinical trials.

PATIENT GROUP

BACKGROUND

Graft versus host disease (GVHD) usually occurs following allogeneic haematopoietic stem cell transplant (HSCT) and is an immunologically mediated inflammatory reaction of donor immune T-cells against proteins, specifically human leukocyte antigens (HLAs), on host cells[3,4]. Although GVHD shares many features with conventional 'rejection' after solid organ transplant, solid organ transplant rejection is caused by an attack on the transplanted tissue by the host immune system, whereas GVHD represents an attack on host tissues by the new transplant-derived immune system. In other words, GVHD has sometimes been

described as the transplant rejecting the rest of the body, rather than the body rejecting the transplant[a].

GVHD occurs and is further triggered by several different molecular phases. Chemotherapy and radiation therapy lead to the production of proinflammatory cytokines (e.g. TNF-α) causing the activation of T-cells through antigen-presenting cells and T-cell interaction, which occurs as a result of the major histocompatibility complex and T-cells binding along with costimulatory signals. This leads to the formation of several different subtype T-cells which traffic through blood vessels to target organs and cause destruction. At this point, the subtype T-cells also recruit other inflammatory cells and cytokines which further promote the cycle of GVHD[5].

There are two main forms of GVHD, acute and chronic, and an overlap syndrome which includes features of both[6]. Acute GVHD is characterised by damage to the skin (>80% of patients with GVHD), gastrointestinal (GI) tract (50-55%) and liver (50%), and usually occurs within 100 days post HSCT. In contrast, chronic GVHD manifests with fibrotic skin disease, bronchiolitis, salivary and lacrimal gland disease, and eosinophilic fasciitis, and typically occurs more than 100 days post HSCT, often following acute GVHD[5,7]. Risk factors for GVHD include age, opposite sex donors, high numbers of T-cells in the donated stem cells or bone marrow, unrelated donor transplants, HLA mismatch, testing positive for cytomegalovirus, and treatment using donor lymphocyte infusion (using donor white blood cells to attack disease) for disease which has recurred[8].

Symptoms of acute GVHD include maculopapular rash, primarily on the palms of the hands and soles of the feet, but can be found on any area of the skin, and is often accompanied by pruritus and tenderness of the affected areas[9]. Liver manifestations of GVHD become apparent through jaundice from hyperbilirubinemia and GI symptoms include diarrhoea (which may include blood), vomiting and nausea[9]. Clinical indications of severe disease include blistering of the skin in an ulcerative nature, and anorexia and/or abdominal pain[6].

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

- Improving Outcomes: A Strategy for Cancer (2011).
- NHS England. 2013/14 NHS Standard Contract for haematopoietic stem cell transplantation (Adult). B04/S/a.

CLINICAL NEED and BURDEN OF DISEASE

It is estimated that between 20% and 80% of patients undergoing an allogeneic HSCT will develop some form of GVHD[8]. Development of acute GVHD is directly related to the level of HLA mismatch, although 40% of patients receiving a HLA-matched transplant will still develop acute GVHD[10]. The incidence of acute GVHD varies widely, ranging from 10-80%, depending on risk factors such as mismatched donors and older age[10]. Approximately 30-70% of allogenic HSCT recipients surviving greater than 100 days post-transplant will develop chronic GVHD within 4-6 months post HSCT[11]. Corticosteroid treatment is recommended in patients with acute GVHD, however this is effective in less than 50%[6,12]. Morbidity and mortality rates continue to rise above 70% in steroid refractory patients with acute GVHD[11]. In 2013-14, there were 1,977 admissions for bone marrow transplant rejection (ICD-10 T86.0) in England, resulting in 6,391 bed days and 2,159 finished consultant episodes[13].

[a] Expert personal opinion.

Based on an estimate of six patients per annum being referred for second line treatment with extracorporeal photopheresis (ECP) in Scotland, it has been estimated that approximately 65 people in England and between 70 and 80 patients in the UK as a whole, would be eligible to receive therapy with remestemcel-L if it were to become standard second line therapy in place of ECP[b,14].

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- None identified.

Other Guidance

- British Committee for Standards in Haematology and the British Society for Bone Marrow Transplantation. Organ-specific management and supportive care in chronic graft-versus-host disease. 2012[15].
- British Committee for Standards in Haematology and the British Society for Bone Marrow Transplantation. Diagnosis and management of chronic graft-versus-host disease. 2012[16].
- British Committee for Standards in Haematology and the British Society for Bone Marrow Transplantation. Diagnosis and management of acute graft-versus-host disease. 2012[12].
- Royal College of Nursing. Graft versus host disease. A guide for families. 2008[17].

CURRENT TREATMENT OPTIONS

Management of GVHD is largely focused on prevention through immunosuppression of donor T-cells with immunomodulatory agents or through depletion of T-cells before or after HSCT using monoclonal or polyclonal antibodies. Immunosuppression is initiated using methotrexate, followed by ciclosporin or tacrolimus therapy post-transplant[5]. In cases of mild acute GVHD, observation is recommended alongside topical steroid for skin manifestations and antihistamines to target pruritus[9,12,18].

Further treatment options for acute GVHD include[5,6,9,11,12,18]:
First line therapy:

- Calcineurin inhibitors.
- Corticosteroids – methylprednisolone or prednisolone at a starting dose of 1-2mg/kg/day based on disease severity, typically taken for a period of 5 days with tapering of dose in patients achieving disease control and with prolonged therapy for patients with GI and liver manifestations of GVHD.
- Non-absorbable steroids – suitable for GI acute GVHD. These help to reduce the dose of systemic steroids.

Second and subsequent line therapy, usually in combination with ciclosporin and corticosteroids – for steroid refractory patients who show signs of worsening acute GVHD in any organ, who have failed to respond after five days of treatment with methylprednisolone and a calcineurin inhibitor, or patients whose symptoms have progressed after 72 hours:

- Antithymocyte globulin – evidence for use in early disease, particularly for skin GVHD.

[b] Expert personal opinion.

- Alemtuzumab – has shown benefit over antithymocyte globulin, but is not specifically licensed for this indication.
- Extracorporeal photopheresis (ECP) – white blood cells from the patient are manipulated *ex vivo* and returned to the patient to induce cellular apoptosis with a high safety profile. This is the most frequent treatment modality used as second line therapy for severe (grade 3 or 4) acute GVHD[c].
- Anti-TNF-α antibodies – infliximab and etanercept, not specifically licensed for this indication, but often preferred for GI GVHD.
- Sirolimus – initiated two to three months post-transplant, followed by maintenance therapy with ciclosporin. Use requires monitoring due to increased risk of thrombotic microangiopathy when used in combination with calcineurin inhibitors.
- Mycophenolate mofetil – however gut toxicity may mimic gut GVHD.
- Interleukin 2 receptor antibodies – basiliximab and others not specifically licensed for this indication, e.g. daclizumab, denileukin diftitox, and inolimomab.

Other agents with a possible role in the management of acute GVHD include pentostatin, MSC therapy and infusion of allogeneic regulatory T-cells. In addition to the above listed treatments, supportive care is essential for patients with acute GVHD, and may include prophylactic antibiotics, gut rest, pain control, sunscreen and nutritional support[5].

EFFICACY and SAFETY

Trial	NCT00562497, 265; Prochymal vs placebo; phase III.	NCT00366145, 280; Prochymal vs placebo; phase III.	NCT00136903, 260-261; Prochymal; phase II.
Sponsor	Mesoblast.	Osiris Therapeutics.	Osiris.
Status	Complete but unpublished.	Published in abstract.	Published.
Source of information	Trial registry[1].	Abstract[19], trial registry[2].	Publication[20], Trial registry[21].
Location	USA, Canada and Australia.	EU (incl UK), USA, Canada, and other countries.	USA.
Design	Randomised, placebo-controlled.	Randomised, placebo-controlled.	Randomised.
Participants	n=184; aged 18 to 70 years; received haematopoietic stem cell transplant using either bone marrow, peripheral blood stem cells or cord blood, or administered a donor leukocyte infusion; newly diagnosed grades B-D acute GVHD; minimum Karnofsky[d] Performance Level at least 30 at study entry; adequate renal function; treated with corticosteroid and Prochymal/placebo within 72 hours of onset of acute	n=244; aged 6 months to 70 years; grades B-D acute GVHD; failure to respond to steroid treatment; minimum Karnofsky[d] Performance Level of at least 30 at study entry; adequate renal function; must receive intervention within 4 days of randomisation.	n=31; aged 18 to 70 years; newly diagnosed grade II-IV acute GVHD requiring therapy; received full or reduced intensity myeloblative regimens followed by an allogeneic haematopoietic stem cell transplant using bone marrow, peripheral blood stem cell, or cord blood; minimum adequate renal and hepatic function.

[c] Expert personal opinion.

[d] Karnofsky/Lansky scores allow patient classification according to function impairment. The lower the score, the worse the survival for most serious illnesses. The Karnofsky scale is designed for subjects 16 years and older; the Lansky scale is used in subjects <16 years of age.

	GVHD.		
Schedule	Randomised to Prochymal $2x10^6$ MSC/kg per infusion; or matching placebo. Each group to receive a total of 6 infusions during the first 4 week of the study: twice weekly during the first 2 weeks then 2 infusions once weekly during the next 2 weeks. All infusions to be given at least 3 days apart.	Randomised to IV Prochymal $2x10^6$ MSC/kg twice a week; or placebo infusions twice a week.	Randomised to IV Prochymal $2x10^6$ MSC/kg (low dose); or Prochymal $8x10^6$ MSC/kg (high dose); each on days 1 and 4.
Follow-up	Active treatment period 4 weeks, follow-up period 90 days.	Active treatment period 4 weeks, follow-up period 180 days.	Active treatment period up to 4 days, follow-up 2 years.
Primary outcomes	Complete response (CR).	CR.	OR; safety.
Secondary outcomes	Overall response (OR).	Survival 180 days post first infusion.	Partial response (PR) or improvement by day 28 in one or more organs involved with GVHD symptoms at day 1; time to best response; time to improvement in one or more organs; survival through study day 90.
Key results	Not reported.	For Prochymal and placebo, respectively: durable CR rates, 35% and 30%, p=0.30; day 100 response rate overall, 82% and 73%, odds ratio (OR) 1.7, p=0.12; day 100 response rate according to organ involvement: skin, 78% and 77% OR=1.1 (95% CI 0.5 to 2.5) p=0.9; liver, 76% and 47%, OR=3.6 (95% CI 1.1 to 11.2) p<0.05; GI tract, 82% and 68%, OR=2.2 (95% CI 1.1 to 4.4) p<0.05.	In total 94% of patients had an initial response, including 77% with CR and 16% with PR. For high dose group and low dose group, respectively: % of patients achieving CR, 66.7 and 87.5; % of patients achieving PR, 33.3 and 0; % of patients achieving no response, 0 and 12.5. 91% of patients did not require subsequent line therapy and were alive at day 90. 9 patients did require subsequent line therapy within 28 days, of whom only 3 survived to day 90 (p=0.0011).
Adverse effects (AEs)	Not reported.	No significant difference in infections reported between treatment arms. For Prochymal and placebo, respectively: recurrent malignancy, 9% and 8%; infusion toxicity, 1.8% and 2.5%; discontinuation due to an	Deaths: 3 patients who achieved CR (causes of death pneumonia, meningitis and aspergillus enteritis); 5 patients who achieved a PR (causes of death progressive GVHD, underlying disease relapse, central nervous system

		AE, 0.6% and 4.6%.	bleed); and 1 patient who achieved no response (cause of death progressive GVHD). 12 grade 3 infections were reported (adenovirus, bacteraemia, cytomegalovirus, viraemia and BK virus-associated cystitis) and 3 grade 4 infections were reported (pseudomonal pneumonia, enteroccocal meningitis and aspergillus enteritis). 3 patients had disease relapse due to second HSCT for acute lymphoblastic leukaemia (ALL), refractory relapsed ALL and Hodgkin's disease.
Expected reporting date	Study completion date previously reported as May 2010.	-	-

ESTIMATED COST and IMPACT

COST

The cost of remestemcel-L is not yet known. However, the cost of the main current comparator, ECP is estimated in excess of £30,000 per patient for treatment over the course of three months[e], with maximum potential costs estimated at £87,000 per patient for the first year[22].

IMPACT - SPECULATIVE

Impact on Patients and Carers

- ☑ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☐ Other:
- ☐ No impact identified

Impact on Health and Social Care Services

- ☐ Increased use of existing services
- ☐ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☑ Other: *new staff training requirements*
- ☐ None identified

Impact on Costs and Other Resource Use

- ☐ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☑ Other increase in costs: *additional staff training required, additional costs for IV administration in clinic*
- ☐ Other reduction in costs:

[e] Expert personal opinion.

☑ Other: *uncertain unit cost compared to existing treatments*

☐ None identified

Other Issues

☑ Clinical uncertainty or other research question identified[f]: *given that the reported efficacy and toxicity of remestemcel-L may be superior to that of ECP, and that ECP is probably the most effective (and certainly the least toxic) second line treatment currently available for acute GVHD, it is likely that the demand for remestemcel-L will be similar to the current demand for ECP.*

☐ None identified

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