Begelomab (Begesand) for steroid resistant acute graft versus host disease

LAY SUMMARY

Graft versus host disease (GvHD) is a condition that occurs when particular types of donated white blood cell attack your own body’s cells. GvHD can occur after a stem cell transplant and can be life threatening. Symptoms include painful rashes, diarrhoea, and vomiting.

Begelomab is a new drug for people whose first treatment for GvHD has failed. Begelomab is given in a drip (directly into a vein).

Begelomab is currently being studied to see how well it works and whether they it is safe to use in people with GvHD. If begelomab is licensed for use in the UK, it could be a new treatment option for patients with GvHD whose first treatment no longer works.

NIHR HSRIC ID: 6306
TARGET GROUP

• Graft versus host disease (GvHD): acute; steroid resistant – second line.

TECHNOLOGY

DESCRIPTION

Begelomab (Begesand; Begedina; BT5/9; SAND-26) is a murine monoclonal antibody directed against CD26 (dipeptidyl peptidase-4). CD26 is important for glucose homeostasis, inactivating incretins such as GLP-1, but it is also an activation marker and costimulatory molecule present in CD4+ helper/memory T cells that accumulate in inflamed tissue. In a mouse model of GvHD, anti-CD26 antibody treatment decreased disease severity and prolonged survival. In a phase II/III trial, begelomab is administered by intravenous (IV) infusion at 2.7mg/m²/day on days 1-5, 10, 14, 17, 21, 24, and 28, for a total of 11 doses. Begelomab does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, begelomab will offer a novel second line treatment option for patients with acute GvHD, who currently have few effective therapies available.

DEVELOPER

Adienne Pharma & Biotech.

AVAILABILITY, LAUNCH OR MARKETING

Begelomab is a designated orphan drug in the EU and USA and is in phase III clinical trials.

PATIENT GROUP

BACKGROUND

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. 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.

GvHD is initiated and then 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. This occurs as a result of the major histocompatibility complex and T cells binding along with costimulatory signals. In turn this causes 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.

There are two main forms of GvHD, acute and chronic, and an overlap syndrome which includes features of both. 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. Risk factors for GvHD include 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.

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

### NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:


### CLINICAL NEED and BURDEN OF DISEASE

In 203-14 1,060 patients in the UK were transplanted with unrelated donor stem cells. It is estimated that up to 80% of patients undergoing an allogeneic HSCT will develop some form of GvHD. 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. The incidence of acute GvHD varies widely, ranging from 10-80% depending on risk factors such as mismatched donors and older age. Approximately 30-70% of allogenic HSCT recipients surviving greater than 100 days post-transplant will develop chronic GvHD within 4-6 months post HSCT.

Corticosteroid treatment is recommended in patients with acute GvHD, however this is effective in less than 50% of cases. Morbidity and mortality rates continue to rise above 70% in steroid refractory patients with acute GvHD. In 2014-15, there were 2,144 admissions for bone marrow transplant rejection (ICD-10 T86.0) in England, resulting in 8,044 bed days and 2,325 finished consultant episodes.

### PATIENT PATHWAY

### RELEVANT GUIDANCE

#### NICE Guidance

- None identified.
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. In cases of mild acute GvHD, observation is recommended alongside topical corticosteroids for skin manifestations and antihistamines to target pruritus.

Further treatment options for acute GvHD include:

**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 acute GvHD affecting the GI tract. These help to reduce the dose of systemic corticosteroids.

**Second and subsequent line therapy**
- Antithymocyte globulin – evidence for use in early disease, particularly for skin GvHD.
- 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.
- 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, mesenchymal stem cell 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 support⁵.

**EFFICACY and SAFETY**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02411084, ADN011, 2015-001360-19, begelomab vs conventional treatment for steroid-resistant acute GvHD; phase II/III.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Adienne.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of information</td>
<td>Manufacturer, trial registry².</td>
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<tr>
<td>Location</td>
<td>EU, USA.</td>
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<td>Design</td>
<td>Randomised, active-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=184 (planned); 18 to 65 years; recipient of allogeneic haematopoietic stem cell transplantation; grade II-IV acute GvHD with failure to respond to corticosteroid treatment; Karnofsky performance ≥50%.</td>
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<td>Schedule</td>
<td>Randomised to begelomab 2.7mg/m² IV as a 1hr infusion on days 1-5, 10, 14, 17, 21, 24, and 28, for a total of 11 doses; or physician’s choice of conventional treatment.</td>
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<td>Follow-up</td>
<td>Active treatment for 28 days, follow-up up to day 365.</td>
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<td>Primary outcome/s</td>
<td>Overall response; transplant-related mortality.</td>
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<td>Expected reporting date</td>
<td>Estimated study completion August 2018.</td>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of begelomab is not yet known. However, the cost of the main current comparator, ECP, is estimated to cost in excess of £30,000 per patient for treatment over the course of three months²¹, with maximum potential costs estimated at £87,000 per patient for the first year²².

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reducing 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: reduced need for ECP.
- Re-organisation of existing services
- Need for new services
- Other: None identified
Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
  - Other: uncertain unit cost compared to existing treatments.
- Other reduction in costs:
  - None identified

Other Issues

- Clinical uncertainty or other research question identified: ECP is probably the most effective (and certainly the least toxic) second line treatment currently available for acute GVHD\(^2\).
- None identified

REFERENCES