# Clinical Commissioning Policy Proposition:

## Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation

Reference: NHS England F01X08/01

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# Clinical Commissioning Policy Proposition: Treatments for Graft versus Host Disease (GvHD) following Haematopoietic Stem Cell Transplantation

First published: March 2016

**Prepared by NHS England Specialised Services Clinical Reference Group for Blood and Marrow Transplantation**

Published by NHS England, in electronic format only.

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## Plain Language Summary

Graft versus host disease (GvHD) is a frequent complication of bone marrow or stem cell transplantation using tissue from another person. (This is called a donor transplant or an allogeneic transplant.) The donor's stem cells contain a type of white blood cell that helps fight infections. GvHD happens when these white blood cell (T cells) attack the recipient’s own tissues. This is because the donated cells (the graft) recognise the recipient’s body cells as foreign, tissue. GvHD may affect different areas of the recipient’s body. Most commonly it affects the skin, digestive system (including the bowel and stomach) and liver.

Treatment starts with systemic corticosteroids. Further treatment is guided by the type of GvHD and includes medicines to suppress the immune system, treating the white blood cells with UVA exposure, and other infusion of specially prepared stem cells.

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of extracorporeal photopheresis (ECP) for patients with acute GvHD and ECP, pentostatin, rituximab and imatinib for patients with chronic GvHD, following stem cell transplantation.

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells for patients with acute GvHD.

## 1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission extracorporeal photopheresis (ECP) for patients with acute GvHD and ECP, pentostatin, rituximab and imatinib for patients with chronic GvHD, and to not routinely commission infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells for patients with acute GvHD, where these patients fall under the remit of specialised commissioning.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether GvHD treatments following stem cell transplantation will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

## 2. The proposed intervention and clinical indication

Graft versus host disease (GvHD) is a complication of allogeneic haematopoietic stem cell transplantation (HSCT) and can be serious and life threatening. GvHD can affect the skin, mouth, eyes, lung, liver and gut. 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 includes other immunosuppressant therapies such as imatinib and sirolimus, newer biological therapies such as rituximab and infliximab and extracorporeal photopheresis (ECP) and cell therapy such as mesenchymal stem cells. Whilst some treatments are complicated by both severe infection and the risk of relapse of the original malignancy by their effect of dampening the immune system, others have a better profile, e.g. ECP.

Clinically, treatment of GvHD is highly individualised, based upon clinical response. There is disparity across England in access to second and subsequent line treatments due to historical contractual arrangements, local availability of ECP, local pricing agreements which permit the use of excluded drugs and differences in funding from CCGs for treatments outside of specialised commissioning.

This policy aims to provide clear definitions of each stage of GvHD, and to review the evidence to define the most clinically effective second-, and third-line non-tariff treatments so that GvHD patients have equal access to appropriate treatments across England. Moreover, this policy applies to all patients who are under the care of NHS England.

## 3. Definitions

Graft versus host disease (GvHD) is a common complication of allogeneic haematopoietic stem cell transplantation which is a 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.

The clinical symptoms of GvHD are variable, depending upon the tissues affected.

- Acute GvHD is characterised by a generalised patchy skin rash, sickness, weight loss, loss of appetite, watery diarrhoea, severe abdominal pain, bloody diarrhoea, and jaundice.

- Chronic GvHD may present with a wider range of symptoms and affect almost any organ, but typically includes symptoms such as alopecia (hair loss), skin thickening and severe rash/erythema of the skin, nail loss, dry mouth and oral lesions, dry eyes, sore muscles and joints, raised liver enzymes, scarring of lung tissue with reduced lung function, pericarditis, and loss of blood cells (red, white, and platelets).

Acute GvHD is graded in severity from I (mild) through II (moderate), III (severe) to IV (very severe) according to the modified Seattle Glucksberg criteria. The grade correlates to survival prognosis with 5-year survival of 25% for grade III and 5% for grade IV disease. (Gratwohl et al, 1995; Cahn et al, 2005)

Chronic GvHD is staged as limited or extensive. Chronic GvHD should be graded as mild, moderate or severe according to the National Institutes of Health (NIH) consensus criteria (Filipovich et al, 2005). Extensive chronic GvHD causes a great degree of morbidity with loss of health and an increased risk of infection. It can be life limiting.

Allogeneic haematopoietic stem cell transplantation (Allo-HSCT) is used to treat carefully selected patients with a range of malignant and non-malignant haematological disorders and other specific disorders of the immune system. It involves replacing the bone marrow stem cells of a patient following high-dose therapy, with stem cells from a tissue-type matched or mismatched donor.

## 4. Aim and objectives

This policy proposition aims to define NHS England's commissioning position for non-tariff treatments as part of the treatment pathway for patients of all ages with GvHD.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for patients with GvHD, and equal access to treatment across England.

## 5. Epidemiology and needs assessment

In 2013 there were 1,615 allogeneic transplants (British Society for Blood and Marrow Transplantation [BSBMT] Register).

The BSBMT Outcomes Register (2007-2012) identifies the rate of acute GvHD (all grades) for all adult allograft recipients ranges from 31-50% depending on stem cell source (2,180 patients, 2007-2012 cohort), whilst the incidence of the most severe Grade 3-4 categories of acute GvHD requiring second or subsequent lines of therapy is below 10% (364 patients, 2007-2012 cohort).

The rate of chronic GvHD in adult allograft recipients ranges from 30-40% (1,592 patients, 2007-2012 cohort) and is 5-6% for extensive chronic GvHD (241 patients, 2007-2012 cohort) who will require second or subsequent lines of therapy.

The rate of acute and chronic GvHD amongst paediatric allograft recipients shows similar incidence compared to adults, and the BSBMT Outcomes Register (2007-2012 cohort) identifies 697 patients with all grades of acute GvHD, whilst the incidence of the most severe Grade 3-4 categories is 134 patients.

In the 2007-2012 paediatric patient cohort, 154 patients have chronic GvHD, while 22 patients have extensive chronic GvHD.

## 6. Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of the following treatments for acute and chronic GvHD following HSCT:

**Acute:** Extracorporeal photopheresis (ECP)

**Chronic:** ECP, pentostatin, rituximab and imatinib

Whilst the clinical evidence is limited and of varying quality, it is recognised that:

- Patients have a high degree of morbidity, particularly those with grade III-IV acute GvHD, making it difficult to gain consent to participate in clinical trials; and
- The low number of patients who might be suitable for this procedure – across a broad range of indications – means that high quality level 1 evidence is unlikely to become available to support the commissioning position.
- The available evidence is relatively consistent in terms of clinical response rates to treatment. This is particularly the case for ECP.

NHS England has concluded that there is not currently sufficient evidence to support a proposal for the routine commissioning of the following treatments for acute GvHD following HSCT: infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells.

**Summary**

A joint working group established by the British Committee for Standards in Haematology (BCSH) and the British Society for Blood and Marrow Transplantation (BSBMT) has reviewed the available literature (as at 2012) concerning the efficacy of available treatments for both acute and chronic GvHD.

A further rapid review of evidence published since then was conducted by the Policy Working Group's Public Health lead to assess any new evidence published since the guidelines.

The tables below summarize the available evidence for each treatment. A more detailed summary of the evidence has been separately provided.

**Acute GvHD**

| Treatment | Outcomes Delivered | Level of Evidence |
|---|---|---|
| Extracorporeal Photopheresis | Improved survival<br>Complete response<br>Immunosuppression discontinuation<br>Good safety profile | A number of prospective cohort studies (>300 patients, across acute and chronic GvHD)<br>Retrospective case series |
| Infliximab | Complete response<br>High risk of infection | Retrospective case series |
| Etanercept | Complete response<br>Partial response | Retrospective case series |
| Inolimomab | Response rate<br>Survival at 20 months | Retrospective case series |
| Alemtuzumab | Response rate<br>Survival at 11 months<br>Range of infectious complications | Retrospective case series |
| Pentostatin | Response rate<br>Median survival<br>Infection rate | Retrospective case series |
| Mesenchymal stem cells | Complete response | Retrospective case series |

**Chronic GvHD**

| Treatment | Outcomes Delivered | Level of Evidence |
|---|---|---|
| Extracorporeal Photopheresis | Improved survival<br>Complete response<br>Immunosuppression discontinuation<br>Good safety profile | One prospective RCT<br>A number of prospective cohort patients, across acute and chronic GvHD)<br>Retrospective case series |
| Pentostatin | Response rate<br>One year survival<br>Two year survival | Two Phase 2 studies<br>One retrospective case series |
| Rituximab | Response rate | Phase 1/2 study<br>Phase 2 study<br>Retrospective study<br>Meta-analysis |
| Imatinib | Response rate<br>18 month survival | Retrospective case series |

## 7. Proposed criteria for commissioning

**Acute GvHD**

NHS England will routinely commission ECP in accordance with the patient pathway (see section 8) for patients meeting the following criteria

**Inclusion criteria:**

(i) Patient presents with continued or relapsed clinical features of acute GvHD (maculopapular rash; persistent nausea and/or emesis; abdominal cramps with diarrhoea; and a rising serum bilirubin concentration) as determined by clinical examination OR biopsy where disease constellation is not clear; AND

(ii) Is unsuitable for, is steroid-dependent OR shows incomplete response to first-line treatment (combination therapy of topical therapies, calcineurin inhibitors, systemic corticosteroids, sirolimus and/or mycophenolate mofetil)

**Exclusion criteria:**

(i) Patients who have previously had nil response to the proposed treatment

**Stopping criteria:**

(i) Patients who do not have a positive response, develop severe toxicity, or for whom the treatment has no effect.

**Chronic GvHD**

NHS England will routinely commission ECP, pentostatin, rituximab and imatinib in accordance with the patient pathway (see section 8) for patients meeting the following criteria

**Inclusion criteria:**

(i) Patient presents with continued or relapsed clinical features of chronic GvHD (depends on organ in which it presents e.g. skin involvement resembling lichen planus or the cutaneous manifestations of scleroderma; dry oral mucosa with ulcerations and sclerosis of the gastrointestinal tract; and a rising serum bilirubin concentration) as determined by clinical examination OR biopsy where disease constellation is not clear; AND

(ii) Is unsuitable for, is steroid-dependent OR shows incomplete response to first-line treatment (combination therapy of systemic corticosteroids, calcineurin inhibitors and/or sirolimus)

**Exclusion criteria:**

(i) Patients who have previously had nil response to the proposed treatment

**Stopping criteria:**

(i) Patients who do not have a positive response, develop severe toxicity, or for whom the treatment has no effect.

## 8. Proposed patient pathway

Patients present with symptoms of either acute or chronic GvHD following allogeneic HSCT. A clinical diagnosis is established with the help of biopsy where the classical constellation of symptoms is not present.

Where, at clinical diagnosis, patients present with signs or symptoms of acute or chronic GvHD in one organ, a further assessment for involvement of other organs is made.

Severity of disease is established using the modified Seattle Glucksberg grading criteria in the case of acute GvHD, and as mild/moderate/severe using the National Institutes of Health (NIH) consensus criteria in the case of chronic disease.

A Multi-Disciplinary 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 acute GvHD, 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. Combination therapies are often required.

**For patients with acute GvHD:**

Topical therapies (incl. hydrocortisone, eumovate, betnovate and dermovate) and optimisation of calcineurin inhibitors (tacrolimus or cyclosporine) and/or mycophenolate mofetil are the preferred approaches in the management of grade I disease. Where patients present with grade II-IV GvHD, systemic corticosteroids (methylprednisolone) are indicated first-line. Dosage varies depending on severity, with 1mg/kg/day indicated for patients with grade II and 2mg/kg/day indicated for patients with grades III-IV disease. Where patients present with acute intestinal GvHD and are at risk of developing adverse effects or becoming corticosteroid dependent, non-absorbable steroids (budesonide or beclomethasone) are indicated to reduce dose of systemic steroids. Combination therapy is common in steroid-refractory patients, with the following treatments indicated: mammalian target of rapamycin inhibitors (sirolimus) and/or mycophenolate mofetil.

Where patients fail to show complete response (i.e. steroid-refractory acute GvHD), have developed significant adverse effects to first-line treatments or are steroid-dependent, ECP should be offered.

**For patients with chronic GvHD:**

Corticosteroids are indicated as first-line treatments, with an initial starting dose of 1mg/kg prednisolone. Where patients are at risk of developing adverse effects or becoming corticosteroid dependent, calcineurin inhibitors (tacrolimus or cyclosporine) are indicated to

reduce dose of systemic steroids.

Where patients fail to show complete response (i.e. steroid-refractory chronic GvHD), have developed significant adverse effects to first-line treatments or are steroid-dependent, sirolimus is indicated. The following treatments are proposed to be added as second-line options (by organ/indication):
1. Refractory chronic GvHD: Pentostatin (1.5mg/m2)
2. Skin, oral, liver and pulmonary chronic GvHD: ECP
3. Refractory cutaneous or musculoskeletal chronic GvHD: Rituximab
4. Refractory pulmonary or sclerodermatous chronic GvHD: Imatinib

ECP should be the second line treatment of choice for skin, oral, liver and pulmonary chronic GvHD. However, ECP is not readily available to all transplant centres and patients are often too sick to travel. For the small proportion for whom ECP may not be suitable, the other treatments set out above should be considered.

Where patients show incomplete response to two different second-line options and/or have developed significant adverse effects, the following treatments are indicated third-line: mycophenolate mofetil, methotrexate and pulsed corticosteroids.

## 9. Proposed governance arrangements

GvHD treatment must be provided in an HSCT unit with available ECP machines. All providers of HSCT must have JACIE accreditation.

The governance arrangements are described in detail in the BMT service specifications for adults and children respectively.

## 10. Proposed mechanism for funding

Treatment to be funded by NHS England. The funding arrangements are described in detail in the service specifications.

It should be noted that the funding arrangements for GvHD are complex. At present, responsibility for funding GvHD sits with NHS England for the first 100 days post-transplant. After this, it transfers to CCGs. This policy proposition applies to all patients who are the responsibility of NHS England specialised commissioning.

## 11. Proposed audit requirements

Complete data must be submitted to the BSBMT registry for all transplants carried out by UK centres. This will enable better evaluation of clinical outcomes broken down by patient and disease-related variables.

All centres must undergo regular JACIE inspection. All centres must also provide the data required for the BMT Quality Dashboard.

Audit requirements are described in more detail in the BMT service specification.

## 12. Documents which have informed this policy proposition

The British Society of Haematology Guidelines for the treatment of GvHD, 2012

## 13. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).