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Feasibility, safety and efficacy of Abatacept for steroid refractory acute graft versus-host disease

J. Yong[1],*, A. Patel[2]
[1]Haematology, Clatterbridge Cancer Centre, Liverpool, UK.
[2]Haematology and Transplant Unit, The Christie NHS Foundation Trust, Manchester, UK.

NHS The Clatterbridge Cancer Centre NHS Foundation Trust

NHS The Christie NHS Foundation Trust

INTRODUCTION

Acute graft-versus-host disease (aGVHD) remains a major limitation to allogeneic haematopoietic stem cell transplantation (HSCT), associated with high patient morbidity and mortality. Steroid refractory aGVHD (SR-aGVHD) has the highest mortality (around 80%) despite treatment intensification with available immunosuppressive therapy. This is complicated by poor response rates alongside increased toxicity and infectious complications from profound immunosuppression and prolonged uncontrolled GVHD. Novel immunotherapeutic strategies are therefore urgently needed for treatment of SR-aGVHD.

Immunological manipulation of T-cell activation is a novel therapeutic treatment approach for aGVHD. Abatacept, a CTLA4-Ig exerting CD28-CD80/CD86 axis T-cell co-stimulation blockade, has been shown in the phase 1 clinical trial setting to be safe, well tolerated without dose limiting toxicities (DLTs), and efficacious in the treatment of heavily pre-treated chronic extensive GVHD. Marked improvement in National Institutes of Health chronic GVHD scores alongside significantly reduced steroid dose requirement in this cohort have led to a phase 2 trial (NCT01954979) and National Comprehensive Cancer Network (NCCN) recommendation. T-cell activation is a key component of aGVHD but it is currently unknown if Abatacept represents a potential therapy for SR-aGVHD.

AIM

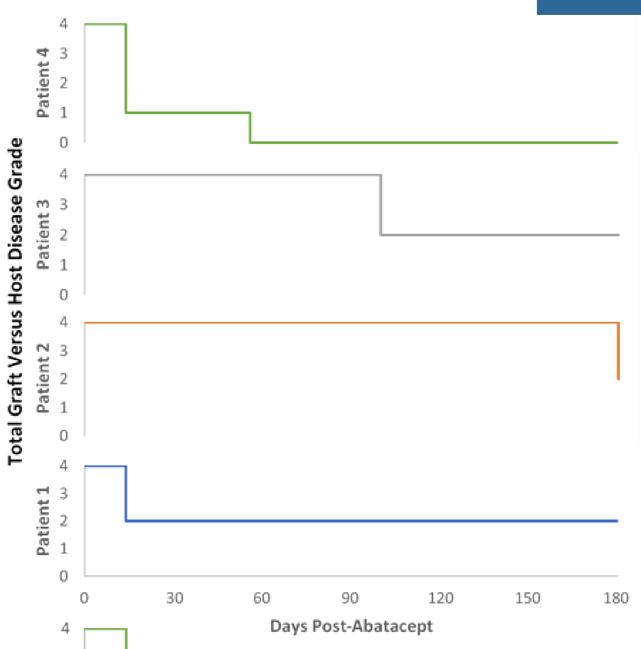
We report the feasibility, safety and efficacy of Abatacept added to the management of SR-aGVHD in a cohort of four heavily pretreated patients in a single centre.

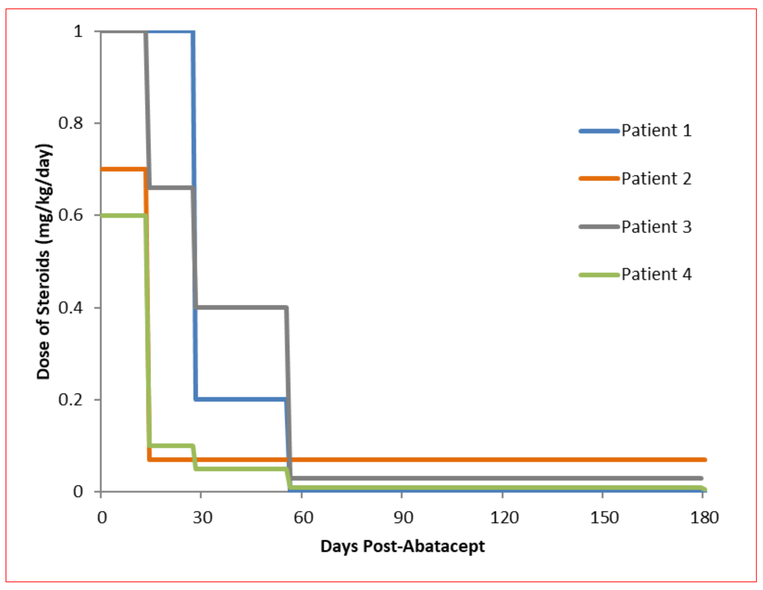
METHODS

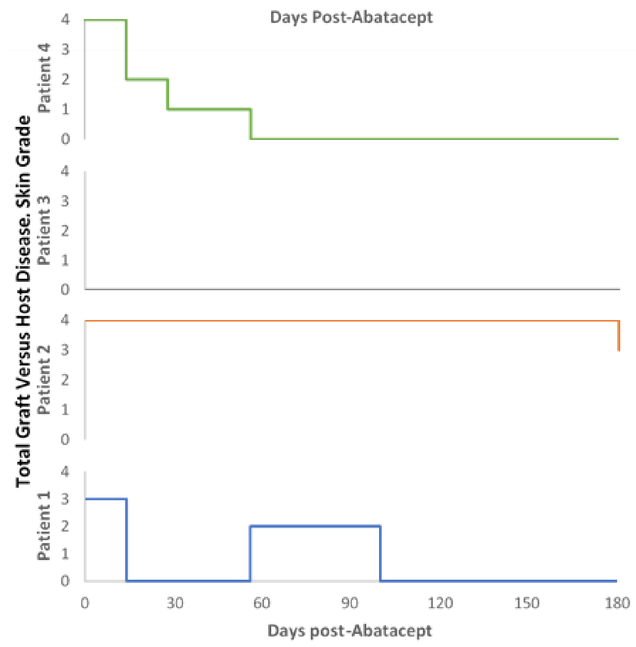
Institutional compassionate access was granted after exhaustion of all available therapies to our cohort of heavily pre-treated patients.

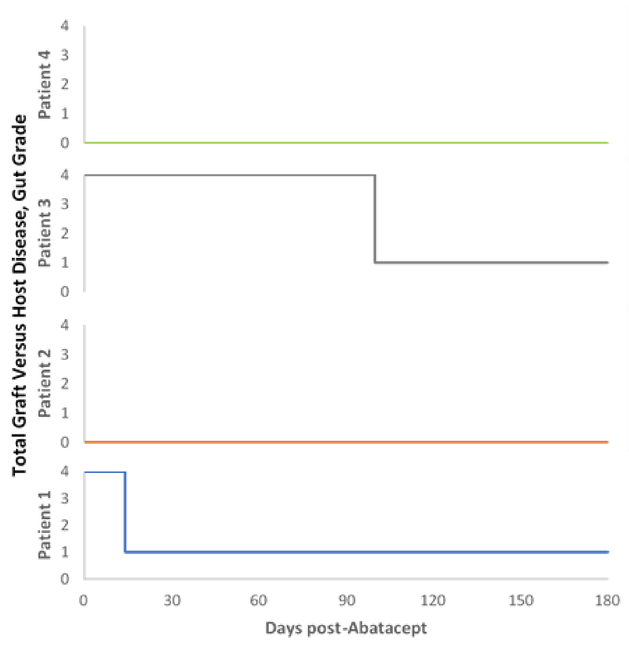
Abatacept 10 mg/kg was administered IV in addition to concurrent treatments for SR-aGVHD at d0, d+14, d+28, d+56, d+72 and d+90. If a clinical response was observed after 6 doses, Abatacept was continued every 4–6 weeks up to 12 doses.

RESULTS









Of our cohort of four patients, three developed aGVHD after donor lymphocyte infusion (DLI), in the absence of pre-DLI conditioning or GVHD prophylaxis. Median overall MAGIC aGVHD score was 4, with two patients having predominant stage 4 gut aGVHD and two patients with predominant stage 4 skin aGVHD. The median prior lines of treatment were 5, including steroid therapy (Prednisolone or Methylprednisolone 2 mg/kg/day), calcineurin and/or mTOR inhibitor (Tacrolimus and/or Sirolimus), mycophenolic acid and extracorporeal photophoresis (ECP) with 8-methoxypsoralen (8-MOP). Patients with gut aGVHD were also treated with vedolizumab and/or infliximab.

Two patients achieved a clinical partial response and one patient a clinical complete response at d+100 after initiation of Abatacept. Importantly all patients achieved a median dose reduction in steroids of 98% by d+100. Three patients had viral reactivation diagnosed prior to Abatacept initiation (median of d155 before Abatacept). Importantly, no new viral reactivations were detected in any patients after Abatacept initiation. No dose limiting toxicities (DLTs) were observed; bacterial infections were not considered a DLT if they had already occurred with prior therapies, being attributed to pre-existing severe immunosuppression and SR-aGVHD. We observed that patients with less than CR by d+100 developed chronic GVHD of the involved organ. Mortality was observed in the two patients with gut involvement, as a result of chronic malnutrition and recurrent immunocompromised infection.

CONCLUSIONS

Our experience suggests that Abatacept for SR-aGVHD is feasible, appears safe and may have efficacy in some patients. A prospective clinical trial is planned.

REFERENCES

1. Blood 2019;134(Suppl_1):4540; https://doi.org/101182/blood-2019-130184

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CONTACT INFORMATION

Corresponding author:
Amit.Patel@christie.nhs.uk