# Adverse events in second- and third-line treatments for acute and chronic graft-*versus*-host disease: systematic review

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***Abstract***

**Background:** Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is associated with an increased risk of graft-*versus*-host disease (GvHD), a strong prognostic predictor of early mortality within the first 2 years following allo-HSCT. The objective of this study was to describe the harm outcomes reported among patients receiving second- and third-line treatment as part of the management for GvHD *via* a systematic literature review.

**Methods:** A total of 34 studies met the systematic review inclusion criteria, reporting adverse events (AEs) across 12 different second- and third-line therapies.

**Results:** A total of 14 studies reported AEs across nine different therapies used in the treatment of acute GvHD (aGvHD), 17 studies reported AEs of eight different treatments for chronic GvHD (cGvHD) and 3 reported a mixed population. Infections were the AE reported most widely, followed by haematologic events and laboratory abnormalities. Reported infections per patient were lower under extracorporeal photopheresis (ECP) for aGvHD (0.267 infections per patient over 6 months) relative to any of the therapies studied (ranging from 0.853 infections per patient per 6 months under etanercept up to 1.998 infections per patient on inolimomab).

**Conclusion:** The reported incidence of infectious AEs in aGvHD and grade 3–5 AEs in cGvHD was lower on ECP compared with pharmaceutical management.

***Keywords:*** extracorporeal photopheresis, graft *versus* host disease, systematic review

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## Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a treatment option for many malignant and non-malignant disorders, including acute leukaemia, lymphoma and aplastic anaemia.[1,2] The European Society of Blood and Marrow Transplantation (EBMT) recently published a survey reporting 17,302 allo-HSCT procedures across 655 centres in 48 countries during 2015 – an increase of 2.1% from 2014.[3] However, allo-HSCT is associated with an increased risk of graft-*versus*-host disease (GvHD), which occurs in approximately 30–70% of transplanted patients.[4,5] This represents a potentially fatal complication; thus, GvHD is a strong prognostic predictor of early mortality within the first 2 years following allo-HSCT.[6]

Approximately 40% of individuals experience acute GvHD (aGvHD) post allo-HSCT. However, this can range from 10% to 80% depending on patient-level risk factors.[1] Clinical manifestations of acute GvHD may include maculopapular rash, elevated serum bilirubin, persistent nausea or abdominal cramping/diarrhoea. By comparison, chronic GvHD (cGvHD) can affect nearly every organ or tissue in the body,[7] occurring in approximately 30–50% of allo-HSCT recipients,[6,8] and may present as a cutaneous scleroderma and/or dry and ulcerated oral mucosa, potentially associated with gastrointestinal tract sclerosis. Similar to acute disease, chronic GvHD is also associated with an elevated serum bilirubin.

The clinical management of both acute and chronic GvHD is challenging due to the relatively high proportion of patients achieving sub-optimal responses on first-line corticosteroids (<50% durable response rate),[9,10] and the higher

mortality risk documented in steroid-refractory GvHD patients.[9,11] Following first-line steroid management, there are a wide range of pharmaceutical agents currently recommended as second- or third-line treatments for aGvHD and cGvHD. Drugs available for aGvHD include interleukin-2 receptor antibodies (e.g., basiliximab, inolimomab), anti-TNF antibodies (e.g., infliximab, etanercept), serine/threonine kinases, mTOR inhibitors (e.g., sirolimus), and immunosuppressant drugs [e.g., mycophenolate mofetil (MMF)].[12] Recommended treatment options for cGvHD are tyrosine kinase inhibitors (e.g., imatinib), mTOR inhibitors (e.g., sirolimus, everolimus), nucleoside analogue (e.g., pentostatin), anti-CD20 monoclonal antibody (rituximab) and immunosuppressant drugs (e.g., MMF).[13,14] Non-pharmaceutical therapies include extracorporeal photopheresis (ECP) – an immunomodulatory therapy currently recommended as a second-line treatment in the British Committee for Standards in Haematology guidelines for both aGvHD and cGvHD.[12,13] In addition, alternate therapeutic options, including mesenchymal stem cells (MSCs) infusion, have shown promise in patients with GvHD secondary to their immunomodulatory function.[15]

Given the uncertainties surrounding the biological basis of both acute and chronic GvHD and the lack of consensus around a standardized treatment approach, the harm profile of available treatments is a particularly important consideration for both healthcare providers and patients when balancing the benefits and risks of competing treatment options for post-allo-HSCT GvHD.[16] Whilst ruxolitinib was approved by the United States (US) Food and Drug Administration (FDA) for steroid-refractory aGvHD in May 2019,[17] standardised recommendations on how to best implement such a diverse array of treatments remain lacking.[18] The objective of this study was to review and describe reported harm outcomes associated with second- and third-line therapies for GvHD following allo-HSCT.

## Materials and methods

### *Search strategy and selection criteria*

The systematic review protocol was developed as per Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and the PRISMA harms checklist.[19,20] A systematic literature search was performed in Medline, Medline In-Process, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) on 15 December 2017. The search strategies used in each database are detailed in the Supplemental File S1. There was no restriction on publication date.

Studies were included if they satisfied the following criteria:

- Patients were diagnosed with either clinician designated aGvHD or cGvHD after stem cell transplantation from any source.
- Patients received any of the following interventions: ECP, basiliximab, inolimomab, etanercept, infliximab, sirolimus, MMF, sirolimus, everolimus, imatinib, pentostatin, rituximab, MSCs, methotrexate, alemtuzumab and ruxolitinib.
- The study reported harms of any type.
- Papers reporting randomised controlled trials (RCTs), non-randomised clinical trials, and cohort studies with prospective or retrospective design were considered for inclusion.
- English language articles or those published in a range of other languages (including Chinese, Croatian, German and Spanish) were considered.

Papers reporting prophylactic use of the intervention, conference proceedings, abstracts, case reports, case series or literature reviews were excluded.

Abstract and full-text screening were conducted by two independent reviewers (R.Z. and V.V.). Inter-rater agreement was assessed *via* kappa statistics.[21] Disagreements were resolved by consensus.

### *Data extraction and quality assessment*

The full-text versions of the included papers were read by a third reviewer (E.M.) who extracted and tabulated relevant data. The data extraction was verified by the second reviewer (V.V.). All included studies were reviewed for reporting causal relations between adverse effects and the treatment of interest. Studies were reviewed for the timing of adverse effects and relation to treatment dosage. Risk of bias across studies was assessed by analysing the reason for study exclusion during the screening of the full-text articles, with the main aim of assessing the extent of

missing information due to selective reporting (Supplemental Table S1).

The overall quality of included studies was assessed using the Jadad scoring system.[22] The risk of individual study bias was assessed using the McMaster Quality Assessment Scale of Harms for primary studies (Supplemental File S2).[23] Future research recommendations are summarised in Supplemental File S3.

Consistent with the PRISMA harms checklist,[20] appropriate terminology and definitions were used throughout this review, with strict differentiation among the following terms: adverse drug reaction, adverse effect, adverse event, complication, harm, safety, side effect and toxicity.

The Common Toxicity Criteria (CTC) of the National Cancer Institute and World Health Organisation (WHO) Toxicity Grading Scale were used to access the severity of AEs when reported by the primary study.[24,25]

### *Statistical analyses*

In studies reporting AEs for included aGvHD treatments, the standardized ratio between the number of AEs and total number of patients at risk was calculated. These were calculated separately for infections, laboratory abnormalities and serious AEs for a defined time horizon (reported follow-up time). Where data to derive the standardized ratio were unavailable, the cumulative incidence of AEs was used as a summary measure. Both approaches were combined to assess the average AE of the treatment of interest. Insufficient data was available across the aGvHD cohort to disaggregate the data by the infectious AE severity. AEs in cGvHD cohorts were summarised as the standardised ratio between the number of AEs grade 3–5 and the total number of patients at risk. Due to the large heterogeneity in patient and disease characteristics across included study populations and the non-standardized reporting of AEs, a meta-analysis was not feasible.

## Results

The literature search of electronic databases generated 6772 hits, 213 of which were selected for full-text review. Following full-text review, 179 papers were excluded based on inclusion and exclusion criteria. A total of 34 studies were included (inter-reviewer agreement; kappa = 0.73). The full selection process is described in Figure 1. Of the 34 papers satisfying the inclusion criteria, 17 articles described treatment for cGvHD, 14 for aGvHD, and 3 for a mix of both sub-populations (Table 1).

### *Acute graft-versus-host disease*

A total of 14 studies covering 664 aGvHD patients reported AEs on therapies used in the treatment of aGvHD (Table 2). Of the nine therapies analysed, reported infections per patient were lower under ECP for aGvHD (0.267 infections per patient over 6 months) relative to any of the pharmaceutical therapies studied (ranging from 0.853 infections per patient per 6 months under etanercept up to 1.998 infections per patient on inolimomab) (Table 2). During 3 months of follow up, 1.639 infectious AEs per patient were reported for etanercept.[6] In the case of MMF, 0.375 infectious AEs were reported after 3 months of follow up.[33] Across 6 months follow up, infectious AEs per patient were reported as; 0.267 for ECP, 0.853 for etanercept, and 1.345 for infliximab.[27,28,31] The cumulative incidences of severe (grade 3–5) infections for etanercept, MMF, and pentostatin were 47%, 80% and 67% respectively (9 months follow up).[30] A single study reported much lower cumulative incidences of severe infections,[32] 44.5% annually for 114 patients treated with MMF. Infectious AEs per patient over 12 months of follow up were reported as 0.739 for basiliximab and 1.998 for inolimomab (Table 2).[39,60]

Severe laboratory abnormalities were reported in the cases of etanercept, MMF and pentostatin,[29,30,32] with a 2-month cumulative incidence of 76%, 79.8/44% and 57%, respectively. These events were reported as absent for ECP, infliximab and basiliximab.[27,31,39]

Serious AEs leading to death were reported as 0.029 per patient for 6 months of follow up for etanercept,[28] and, for the same period, 0.134 serious AEs leading to sepsis per patient for ECP (Table 2).[27] At 1 year of follow up, serious AEs leading to death were reported as 0.174 per patient for basiliximab and 0.531 for inolimomab.[39,60] In addition to the prospective studies reviewed, a retrospective cohort study was included. The study conducted a comparison of AEs among MMF, inolimomab and etanercept, reporting a hazard of

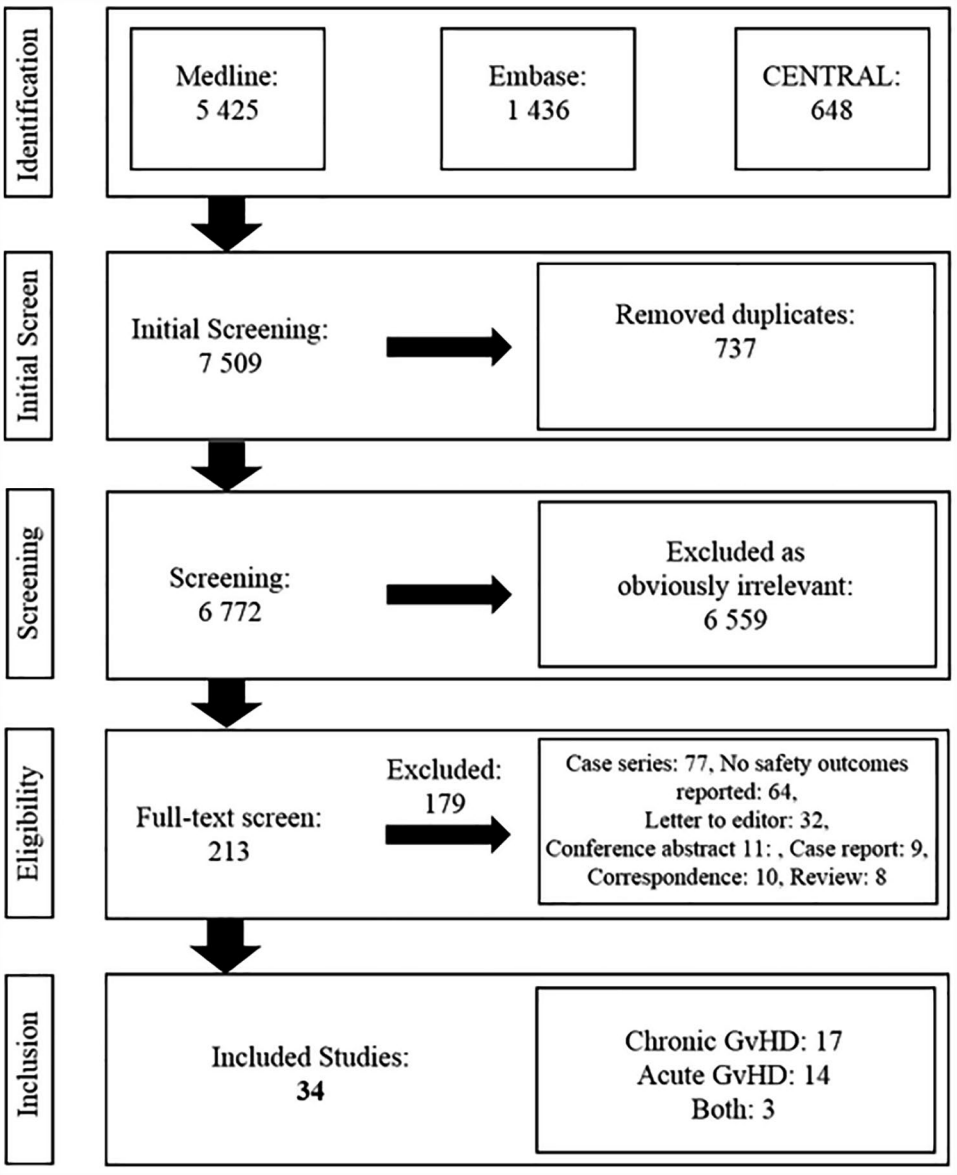


**Figure 1.** PRISMA flow chart of articles included in this systematic review.
CENTRAL, Cochrane central register of controlled trials; GvHD, graft-*versus*-host disease; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCTs, randomised controlled trials.

bacterial infection of 2.84 and 3.26 times higher in patients treated with inolimomab and etanercept, respectively, relative to patients treated with MMF.[34] These observations were consistent with the prospective studies.

### *Chronic GvHD*

A total of 17 studies covering 560 cGvHD patients met the inclusion criteria and reported AEs of eight different treatments for cGvHD (Table 3). The reported incidence of severe AEs in patients receiving ECP treatment for cGvHD (0.12 over 3 months; 0.480 AEs per patient annualised) was lower than that observed for either alemtuzumab (1.155 per 3 months), imatinib (upper range 1.17 per 3 months) or MMF (1.09 AEs per patient per 3 months).[41,42] The event rate in patients receiving ECP was further lower relative to low-dose imatinib (200 mg) 0.59 grade 3–5 AEs per patient across 3 months (Table 3).[43,44,46,47,61] However, a strong dosage related toxicity was observed across several

**Table 1.** Overview of all included studies for aGvHD and cGvHD.

| Treatment | Study (author) | Country | Study period | Study design | Data collection | N patients | N patients of interest | Population | GvHD grade | Age (range) | Male (%) | Harm outcome as primary objective | Harm outcomes defined | Grading system applied | Funding source |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **aGvHD** | | | | | | | | | | | | | | | |
| Alemtuzumab | Khandelwal *et al.*[26] | US | 2012–2014 | Cohort study | Prospective | 15 | 15 | Mix | n.r. | 10 (1.4–27) | n.r. | No | No | No | n.r. |
| ECP | Calore *et al.*[27] | Italy | 1999–2005 | Cohort study | Prospective | 31 | 15 | Paediatric | 2–4 | 9.6 (1.4–18.1) | 56 | No | No | No | Non-industry funders |
| Etanercept | Gatza *et al.*[28] | US | 2008–2013 | Clinical trial, phase II | Prospective | 34 | 34 | Mix | 1 | 51 (10–67) | 76.5 | No | No | No | Non-industry funder |
| | Levine *et al.*[29] | US | 2001–2006 | Clinical trial, phase II | Prospective | 160 | 61 | Mix | 2–4 | 51 (7–65) | n.r. | No | No | No | Industry and non-industry funders |
| | Alousi *et al.*[30] | US | 2005–2008 | Multicentre, randomized, phase II trial | Prospective | 180 | 46 | Mix | 0–4 (majority 2–3) | 50 (8–70) | 65 | No | Yes | Yes, CTC NCI v3 | Industry and non-industry funders |
| Infliximab | Couriel *et al.*[31] | US | 2000–2003 | Single-centre, open label phase III | Prospective | 57 | 29 | Adult | 2–4 | 49 (22–65) | 58.6 | Yes | Yes | Yes, CTC NCI v2 | Industry funder |
| MMF | Bolanos-Meade *et al.*[32] | US | 2010–2011 | Multicentre RCT, phase III trial | Prospective | 235 | 116 | Mix | 1–4 | 54 (9.1–76.3) | 61.2 | No | Yes | Yes, CTC NCI v3 | Non-industry funders |
| | Jacobson *et al.*[33] | US | n.r. | Multicentre RCT, phase II trial | Prospective | 45 | 45 | Mix | 1–3 | 41 (mean) (SD 13.6) | n.r. | No | Yes | Yes, CTC NCI v3 | Industry and non-industry funders |
| | Alousi *et al.*[30] | US | 2005–2008 | Multicentre, randomized, phase II trial | Prospective | 180 | 45 | Mix | 0–4 (majority 2–3) | 42 (13–63) | 62 | No | Yes | Yes, CTC NCI v3 | Industry and non-industry funders |
| | Xhaard *et al.*[34] | France | 1999–2010 | Cohort study | Retrospective | 93 | 52 | Mix | 1–4 | 30 (5–58) | 60 | No | No | No | n.r. |
| MSC | Boome *et al.*[35] | The Netherlands | 2009–2012 | Clinical trial | Prospective | 48 | 48 | Mix | 2–4 | 44.9 (1.3–68.9) | 65 | Yes | No | No | Non-industry funders |
| | Zhao *et al.*[36] | China | 2010–2013 | Clinical trial | Prospective | 47 | 28 | Mix | 2–4 | 26 (14–54) | 67.8 | No | No | Yes, CTC NCI v3 | Non-industry funders |
| | Baygan *et al.*[37] | Sweden | 2011–2014 | Cohort study | Retrospective | 44 | 34 | Mix | 2–4 | 49 (1–68) | 58.8 | Yes | Yes | No | Non-industry funders |
| | Kebriaei *et al.*[38] | US | 2005–2006 | Clinical trial | Prospective | 31 | 31 | Adult | 2–4 | 52 (34–67) | 67.7 | No | No | No | Industry funder |
| Pentostatin | Alousi *et al.*[30] | US | 2005–2008 | Multicentre, randomized, phase II trial | Prospective | 180 | 42 | Mix | 0–4 (majority 2–3) | 53 (24–68) | 64 | No | Yes | Yes, CTC NCI v3 | Industry and non-industry funders |

*(Continued)*

**Table 1.** (Continued)

| Treatment | Study (author) | Country | Study period | Study design | Data collection | N patients | N patients of interest | Population | GvHD grade | Age (range) | Male (%) | Harm outcome as primary objective | Harm outcomes defined | Grading system applied | Funding source |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Basiliximab | Schmidt-Hieber *et al.*[39] | Germany | 1999–2004 | Clinical trial, phase II | Prospective | 23 | 23 | Adult | 2–3 | 51 (31–63) | 57 | Yes | Yes | Yes, CTC NCI v3 | n.r. |
| **cGvHD** | | | | | | | | | | | | | | | |
| Alemtuzumab | Nikiforow *et al.*[40] | US | 2007–2011 | Phase I trial | Prospective | 13 | 13 | Adult | Mild - severe | 55 (35–67) | 61.5 | Yes | Yes | Yes, CTC NCI v3 | Industry and non-industry funder |
| ECP | Flowers *et al.*[41] | International | 2002–2005 | RCT, phase II | Prospective | 95 | 48 | Mix | n.r. | 41 (16–67) | 59 | No | Yes | No | Industry funder |
| | Greinix *et al.*[42] | Austria | 2003–2006 | Open label crossover trial | Prospective | 29 | 29 | Adult | n.r. | 43 (20–67) | 48 | Yes | Yes | No | Industry funder |
| Imatinib | Baird *et al.*[43] | US | 2008–2011 | Open-label pilot phase II trial | Prospective | 20 | 20 | Mix | n.r. | 51.5 (7–60) | 70 | No | Yes | No | Non-industry funders |
| | Chen *et al.*[44] | US | 2008–2009 | Clinical trial, phase I | Prospective | 15 | 15 | Adult | n.r. | 45 (20–68) | 66.6 | Yes | Yes | Yes | Industry and non-industry funder |
| | Arai *et al.*[45] | US | 2011–2014 | RCT Crossover design | Prospective | 72 | 35 | Adult | n.r. | 56 (19–72) | 51 | No | No | Yes, n.r. | Industry funders |
| | Olivieri *et al.*[46] | Italy | n.r. | Clinical trial | Prospective | 19 | 19 | Mix | n.r. | 29 (10–62) | 52.6 | Yes | Yes | Yes, WHO scale | Non-industry funders |
| | Olivieri *et al.*[47] | Italy | 2008–2011 | Multicentre phase 2 study | Prospective | 39 | 39 | Adult | n.r. | 48 (28–73) | 68 | Yes | Yes | Yes, WHO scale | Non-industry funders |
| MMF | Martin *et al.*[48] | US | 2004–2008 | RCT | Prospective | 157 | 74 | Mix | n.r. | n.r. | 55 | No | Yes | No | Industry and non-industry funders |
| MSC | Jurado *et al.*[49] | Spain | n.r. | Phase I/II trial | Prospective | 14 | 14 | Adult | Moderate - severe | 48 (24–60) | 50 | Yes | Yes | No | Non-industry funders |
| Pentostatin | Jacobsohn *et al.*[50] | US | n.r. | Phase II trial | Prospective | 58 | 58 | Mix | n.r. | 33 (5–64) | 60.3 | Yes | Yes | Yes, CTC NCI v3 | Industry funders |
| | Jacobsohn *et al.*[51] | US | n.r. | Phase II trial | Prospective | 51 | 51 | Paediatric | n.r. | 9.8 (0.9–20.7) | 53 | Yes | Yes | Yes, CTC NCI v3 | Industry funders |

*(Continued)*

**Table 1.** (Continued)

| Treatment | Study (author) | Country | Study period | Study design | Data collection | N patients | N patients of interest | Population | GvHD grade | Age (range) | Male (%) | Harm outcome as primary objective | Harm outcomes defined | Grading system applied | Funding source |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rituximab | Malard *et al.*[52] | France | 2008–2012 | Multicentre, phase II trial | Prospective | 24 | 24 | Adult | 0–3 | 47 (23–63) | 71 | No | No | No | Industry non-industry funders |
| | Cutler *et al.*[53] | US | 2004–2005 | Open-label, phase I/II study | Prospective | 21 | 21 | Adult | 0–4 | 42 (21–62) | 48 | No | Yes | Yes, CTC NCI | Industry non-industry funders |
| | Kim *et al.*[54] | Korea | n.r. | Multicentre, open label, phase II trial | Prospective | 37 | 37 | Mix | n.r. | 29 (8–57) | 54.1 | No | No | Yes, n.r. | n.r. |
| | Teshima *et al.*[55] | Japan | 2006–2007 | Open-label phase II study | Prospective | 7 | 7 | Adult | 1–2 | 48 (24–55) | 71 | Yes | Yes | Yes, CTC NCI v 3 | Non-industry funder |
| | Arai *et al.*[45] | US | 2011–2014 | RCT crossover design | Prospective | 72 | 37 | Adult | n.r. | 56 (21–78) | 59 | No | No | Yes, n.r. | Industry funders |
| Sirolimus | Johnston *et al.*[56] | US | n.r. | Clinical trial, phase II | Prospective | 19 | 19 | Adult | n.r. | 41 (23–57) | n.r. | No | Yes | Yes, CTC NCI | Non-industry funders |
| **Mixed aGvHD/cGvHD** | | | | | | | | | | | | | | | |
| ECP | Messina*et al.*[57] | Italy | 1992–2000 | Cohort study | Retrospective | 77 | 77 | Paediatric | 2–4 | 8.9 (0.3–20.5) | 72.7 | Yes | Yes | No | Non-industry funders |
| MMF | Basara *et al.*[58] | Germany | n.r. | Cohort study | Prospective | 51 | 30 | n.r. | 1–4 | n.r. | n.r. | Yes | Yes | No | n.r. |
| MSC | Hermann *et al.*[59] | Australia | 2007–2010 | Phase I trial | Prospective | 19 | 19 | Adult | 2–4 | 48 (21–61) | 68 | Yes | Yes | No | Non-industry funders |

aGvHD, acute graft *versus* host disease; cGvHD, chronic graft *versus* host disease; CTC, common toxicity criteria of the National Cancer Institute; ECP, extra corporeal photopheresis; MMF, mycophenolate mofetil; MSC, mesenchymal stem cells; n.a., not applicable; n.r., not reported; RCT, randomised controlled trial; US, United States; WHO, World Health Organisation toxicity grading scale.

**Table 2.** AEs in patients with aGvHD.

| Study (author) | AE type | Follow up | *n* patients | Number of AE events | Dosage, mode of use, AEs causal relation to treatment | AE severity | AE per subject | Summary |
|---|---|---|---|---|---|---|---|---|
| **Alemtuzumab** | | | | | | | | |
| Khandelwal *et al.*[26] | Bacterial | 6 months | 15 | 10 | 1 mg/kg (maximum dose 43 mg) over 5 days. Additional 0.2 mg/kg on days, 7, 10, 15 and 22. Subcutaneous injection. Most common AEs related to alemtuzumab reported. | n.r. Three dead, 1 from sepsis and 2 from viral infection. | 0.666/6 months | Number of patients: 15 Infections per patient: 2.665/6 months LA per patient: 0.800/6 months |
| | Fungal | | | 4 | | | 0.266/6 months | |
| | Viral | | | 26 | | | 1.733/6 months | |
| | Laboratory abnormalities | | | 12 | | | 0.800/6 months | |
| **ECP** | | | | | | | | |
| Calore *et al.*[27] | Bacterial | 6 months | 15 | 2 | 2 consecutive days at 1-week intervals for the first month, then every 2 weeks during the second and third months and then monthly for at least another 3 months. Average duration 180–240min. Causal relation of treatment with AEs not reported. | All bacterial with septic episodes | 0.134/6 months | Number of patients: 15 Infections per patient: 0.267/6 months Serious AEs: 0.134/6 months |
| | Fungal | | | 1 | | n.r. | 0.067/6 months | |
| | Viral | | | 1 | | n.r. | 0.067/6 months | |
| **Etanercept** | | | | | | | | |
| Gatza *et al.*[28] | Bacterial | 6 months | 34 | 10 | 0.4 mg/kg, maximum 25 mg/dose. Subcutaneous application, twice weekly on non-consecutive days for 4 weeks, for a total of 8 doses Causal relation of treatment with AEs not reported. | n.r. One dead caused by the infection | 0.294/6 months | Number of patients: 141 Infections per patient:0.853/6 months and 1.639/3 months Serious AEs per patient: 0.0294/6 months Grade 3–5 CI of infection: 47%/9 months Grade 3–5 CI of LA:76%/2 months |
| | Fungal | | | 1 | | | 0.029/6 months | |
| | Viral | | | 18 | | | 0.529/6 months | |
| Levine *et al.*[29] | Bacterial | 3 months | 61 | 64 | 0.4 mg/kg (maximum dose 25 mg) twice weekly for 8 weeks. Subcutaneous injection. Causal relation of treatment with AEs not reported. | n.r. | 1.049/3 months | |
| | Fungal | | | 17 | | | 0.278/3 months | |
| | Viral | | | 19 | | | 0.312/3 months | |

*(Continued)*

**Table 2.** (Continued)

| Study (author) | AE type | Follow up | *n* patients | Number of AE events | Dosage, mode of use, AEs causal relation to treatment | AE severity | AE per subject | Summary |
|---|---|---|---|---|---|---|---|---|
| Alousi *et al.*[30] | Infections | 9 months | 46 | – | Patients with BSA of $> 0.6\,m^2$ received a dose of 0.4 mg/kg (maximum dose of 25 mg). Subcutaneous injection twice weekly for 4 weeks All grade 3–5 toxicities are reported regardless of attribution to drug | 47% | – | |
| | Laboratory abnormalities | 2 months | | – | | 76% | – | |
| **Infliximab** | | | | | | | | |
| Couriel *et al.*[31] | Bacterial | 6 months | 29 | 18 | 10 mg/kg Intravenous application 2 h weekly for 4 weeks AEs reported as a therapy-related toxicity | 51% | 0.621/6 months | Number of patients: 29 Infections per patient: 1.345/6 months LA per patient: 0 CI of infections 51% |
| | Fungal | | | 8 | | | 0.276/6 months | |
| | Viral | | | 13 | | | 0.448/6 months | |
| | Laboratory abnormalities | | | 0 | | 0 | 0/6 months | |
| **Inolimomab** | | | | | | | | |
| Socie *et al.*[60] | Bacterial | 12 months | 49 | 40 | Intravenous dose of 0.3 mg/kg per day for induction phase (days 1–8), then days 9–16 if needed. 0.2 mg/kg per day for maintenance. Maximum injection period was 29 days. | n.r. | 0.816 | Number of patients: 49 Infections per patient: 1.998/year Grade 3–5 AEs: 1.000/year |
| | Fungal | | | 17 | | | 0.346 | |
| | Viral | | | 38 | | | 0.775 | |
| | Parasitic | | | 3 | | | 0.061 | |
| | Serious AEs | | | 49 | | | 1.000 | |
| **MSC** | | | | | | | | |
| Herrmann *et al.*[59] | Vital signs and infusional reactions | n.r. | 12 | 0 | 8 intravenous infusions of MSC twice weekly for 4 weeks. If CR was not achieved retreatment with two infusions at weekly intervals. | n.r. | – | Number of patients: 155 Infections per patient: 1.219/year and 0.484/3 months Serious AEs: 1.5/year AEs related to infusions: 0.087/8 months |
| Boome *et al.*[35] | Serious AEs | 12 months | 50 | 75 | $1–2 \times 10^6$ cells/kg bodyweight Infusion at day, 0, 8 and 22. Additional dose at 8 weeks if CR was not reached. | n.r. | 1.500 | |
| | Infections | | | 36 | | | 0.720 | |

*(Continued)*

**Table 2.** (Continued)

| Study (author) | AE type | Follow up | *n* patients | Number of AE events | Dosage, mode of use, AEs causal relation to treatment | AE severity | AE per subject | Summary |
|---|---|---|---|---|---|---|---|---|
| Zhao *et al.*[36] | Bacterial | 12 months | 28 | 5 | 1–2 × $10^6$ cells/kg bodyweight Infusion once a week until CR was reached, or until 8 doses had been administered. | n.r. | 0.178 | |
| | Fungal | | | 0 | | | 0 | |
| | Viral | | | 4 | | | 0.143 | |
| | Mixed infection | | | 5 | | | 0.178 | |
| Baygan *et al.*[37] | Fever | 8 months | 34 | 1 | 1.5 (0.9–2.9) × $10^6$ viable DSCs/kg. Patients were given median 2 (range 1–5) doses | n.r. | 0.029/8 months | |
| | Headache and dyspnoea | | | 1 | | | 0.029/8 months | |
| | Vertigo | | | 1 | | | 0.029/8 months | |
| Kebriaei *et al.*[38] | Infections | 3 months | 31 | 15 | 2 × $10^6$ MSCs/kg (low dose) or 8 × $10^6$ MSCs/kg (high dose) First infusion 24–48 after aGvHD onset, second dose 3 days later. | n.r. | 0.484/3 months | |
| **MMF** | | | | | | | | |
| Bolanos-Meade *et al.*[32] | Infections | 12 months | 116 | – | 1000 mg or 20 mg/kg (for patients, 60 kg) Orally or IV every 8 h All toxicities were reported regardless of relation to the treatment | 44.5% | – | Number of patients: 193 Infections per patient: 0.375/3 months CI of serious AEs: 2.6%/year Grade 3–5 CI of infection: 80%/9 months and 44.5%/year Grade 3 to 5 CI of LA: 44% and 79.8%/two months |
| | Laboratory abnormalities | 2 months | | – | | 79.8% | – | |
| | Serious AEs | 12 months | | – | | 2.6% | – | |
| Jacobson *et al.*[33] | Bacterial | 3 months | 32 | 3 | 20 g/kg in patients with a body surface area (BSA) > 1.5 $m^2$ (maximum 1 g twice daily) and 750 mg in those with a BSA < 1.5 $m^2$ Twice daily orally or IV Causal relation of treatment with harms not reported | n.r. | 0.094/3 months | |
| | Fungal | | | 1 | | n.r. | 0.031/3 months | |
| | Viral | | | 8 | | n.r. | 0.25/3 months | |

*(Continued)*

**Table 2.** (Continued)

| Study (author) | AE type | Follow up | *n* patients | Number of AE events | Dosage, mode of use, AEs causal relation to treatment | AE severity | AE per subject | Summary |
|---|---|---|---|---|---|---|---|---|
| Alousi *et al.*[30] | Infections<br>Laboratory abnormalities | Nine months<br>2 months | 45 | –<br>– | Twice daily orally or intravenously All grade 3–5 adverse events are reported regardless of attribution to drug | 80%<br>44% | –<br>– | |
| **Pentostatin** | | | | | | | | |
| Alousi *et al.*[30] | Infections<br>Laboratory abnormalities | 9 months<br>2 months | 42 | –<br>– | 20 mg/kg if BSA $>$ 1.5 $m^2$ (maximum dose of 1 g twice daily), 750 mg intravenously/orally twice daily if BSA was 1.25–1.5 $m^2$ or 600 mg/$m^2$ patients $<$1.5 $m^2$ Twice daily orally or intravenously All grade 3–5 toxicities are reported regardless of attribution to drug | 67%<br>57% | –<br>– | Number of patients: 42 Grade 3–5 CI of infection: 67%/9 months Grade 3–5 CI of LA: 57%/2 months |
| **Basiliximab** | | | | | | | | |
| Schmidt-Hieber *et al.*[39] | Bacterial<br>Fungal<br>Viral<br>Laboratory abnormalities | 12 months | 23 | 10<br>2<br>5<br>0 | 20 mg on days 1 and 4. The solution was administered over a period of 30 min without premedication. Toxicity connected to treatment. Fungal infections accessed as proven or possible according to EORTC criteria. | n.r.<br>n.r.<br>n.r.<br>n.r. | 0.435<br>0.087<br>0.217<br>0 | Number of patients: 23 Infections per patient: 0.739/year Serious AEs: 0.174/year (exitus letalis) LA: 0 |

AEs, adverse events; aGvHD, acute graft *versus* host disease; CI, cumulative incidence; BSA, body surface area; EORTC, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group; LA, Laboratory abnormalities; n.a., not applicable; n.r., not reported.

**Table 3.** AEs in patients with cGvHD.

| Study (author) | AE type | Follow up | Number of patients | Dosage, AE causal relation to treatment | AE severity grade 3–5 event/patient | Summary |
|---|---|---|---|---|---|---|
| **Alemtuzumab** | | | | | | |
| Nikiforow *et al.*[61] | Bacterial<br>Viral<br>Hematologic | 12 months | 13 | Three times during week, 1 once a week for 3 weeks after. Three dose levels: 3 mg, 10 mg, maximum 30 mg. | 0.462<br>0.385<br>0.308 | Number of patients: 13 AE severity grade 3–5 per patient: 1.155/year |
| **ECP** | | | | | | |
| Flowers *et al.*[41] | Mainly AEs led to withdrawal of ECP | 3 months | 48 | Three times during week 1 Twice weekly on consecutive days during weeks 2 through 12. | 0.13 | Number of patients: 77 AE severity grade 3–5 per patient: 0.12/three months |
| Greinix *et al.*[42] | Mainly infections and vascular access problem | 3 months | 29 | n.r. | 0.10 | |
| **Imatinib** | | | | | | |
| Olivieri *et al.*[46] | Mostly laboratory abnormalities, hematologic and infectious AEs | 6 months | 19 | 100 mg/day for 6 months, increased to 200 mg after 1 month, 400 mg after 3 months | 0.26 | Number of patients: 128 AE severity grade 3–5 per patient: 0.26 to 1.17 |
| Olivieri *et al.*[47] | Mostly laboratory abnormalities, infectious and gastrointestinal AEs | 3 months | 39 | 100 mg/day during the first 15 days Maximum 400 mg | 0.59 | |
| Baird *et al.*[43] | Mostly laboratory abnormalities and gastrointestinal AEs | 6 months | 20 | Adverse events - dose related Final dose of 100–300 mg daily | 0.9 | |
| Chen *et al.*[44] | Gastrointestinal and musculoskeletal AEs | 14 months | 15 | Adverse events - dose related Grade 2–5 AEs more frequent on 400 mg than 200 mg daily | 1.17–400 mg<br>0.4–200 mg | |
| Arai *et al.*[45] | Mostly infections and laboratory abnormalities | 19.5 months | 35 | 200 mg daily | 0.54 | |
| **MSC** | | | | | | |
| Herrmann *et al.*[59] | Vital signs and infusional reactions | n.r. | 7 | 8 intravenous infusions of MSC twice weekly for 4 weeks. If CR was not achieved retreatment with two infusions at weekly intervals. | – | Number of patients: 21 Serious AE per patient (low dose group): 0.214/year<br>Serious AE per patient (high dose group): 0.5/year |

*(Continued)*

**Table 3.** (Continued)

| Study (author) | AE type | Follow up | Number of patients | Dosage, AE causal relation to treatment | AE severity grade 3–5 event/patient | Summary |
|---|---|---|---|---|---|---|
| Jurado *et al.*[49] | Mostly laboratory abnormalities, hematologic and infectious AEs | 12 months | 14 | Group A: $1 \times 10^6$ /kg MSC | 0.214 | |
| | | | | Group B: $3 \times 10^6$ /kg MSC | 0.500 | |
| **MMF** | | | | | | |
| Martin *et al.*[48] | Permanent or temporary withdrawal of MMF and infections | 3 months | 74 | 750–1000 mg, orally, twice daily | 1.09 | Number of patients: 74 AE severity grade 3–5 per patient: 1.09/3 months |
| **Pentostatin** | | | | | | |
| Jacobsohn *et al.*[50] | Mostly infections | 19 months | 58 | 4 mg/m$^2$ Intravenous infusion during 20–30 min every 2 weeks | 0.29 | Number of patients: 109 AE severity grade 3–5 per patient: 0.29–0.69 |
| Jacobsohn *et al.*[51] | Mostly infections | 6 months | 51 | | 0.69 | |
| **Rituximab** | | | | | | |
| Malard *et al.*[52] | Infections | 12 months | 24 | 375 mg/m$^2$ Weekly for 4 consecutive weeks | 0.312 | Number of patients: 126 AE severity grade 3–5 per patient: 0.14–0.48 annually |
| | Other | | | | 0.166 | |
| Cutler *et al.*[53] | Mostly infections | 12 months | 21 | | 0.43 | |
| Kim *et al.*[54] | Infections only | 12 months | 37 | | 0.19 | |
| Teshima *et al.*[55] | Infections only | 12 months | 7 | | 0.14 | |
| Arai *et al.*[45] | Mostly laboratory abnormalities and infections | 19.5 months | 37 | | 0.46 | |
| **Sirolimus** | | | | | | |
| Johnston *et al.*[56] | Mostly infections and haematological | 9 months | 24 | 10 mg oral loading followed by 5 mg/day | 0.53 | Number of patients: 24 AE severity grade 3–4 per patient: 0.53 |

AEs, adverse events; cGvHD, chronic graft versus host disease; LA, laboratory abnormalities; MMF, mycophenolate mofetil; n, number; n.a. not applicable; n.r., not reported.

imatinib studies. When imatinib was reduced to a dosage of 100 mg, an average of 0.26 severe AEs per patient within 6 months of follow up was observed.[46] For the same follow-up period, higher doses of imatinib (up to 300 mg) resulted in an average of 0.9 severe AEs per patient,[43] increasing to 1.17 AE per patient when the dosage is scaled up to 400 mg over 14 months of follow up.[44]

One study reporting AEs during MMF treatment did not report treatment related AEs but rather overall AEs.[48] Thus, the 1.09 AEs per patient within 3 months of follow up likely represents a significant overestimation for MMF (Table 3). In two studies reporting pentostatin therapy, there was a higher AE rate per patient at 6 months (paediatric population) compared with that at 19 months of follow up (0.29 *versus* 0.69 per patient combined across both studies).[50,51] In one study of patients treated with sirolimus, the number of AEs per patient was 0.53 over a 9-month follow-up period (Table 3).[56]

Two studies of rituximab treatment reported a small rate of AEs per patient, from 0.14 to 0.19 per year.[54,55] Those results differed from other studies where AEs per patient were 0.43 at 12 months and 0.46 at 19.5 months of follow up (Table 3).[54,61]

### *Mixed population of aGvHD and cGvHD*

Three studies covering 126 patients reported a mixed study population across three different therapies: ECP, MSC and MMF. In one of these studies, AEs were reported separately for each indication (Tables 2 and 3).[59] No infusion-related toxicities attributable to MSC treatment were reported amongst the patient population. However, two studies only reported results for the combined cohort.[58,57] One study reported 0.061 central line infections per patient at 6 months of follow up, and a 64% cumulative incidence of mild hypotensive events during ECP treatment.[57] The second study reported 0.499 hematologic and 0.133 gastrointestinal AEs per patient during MMF treatment, although follow-up time was not stated.[62]

## Discussion

Across included studies, infections were the most frequently reported AE on second- and third-line treatments for GvHD. Reported infection rates were lower under ECP management of aGvHD relative to any of the pharmaceutical treatments analysed (standardised per patient per unit of time). Severe AEs were also lower when ECP was used in cGvHD relative to other therapeutic treatments.

Furthermore, ECP treatment was associated with the lowest observed standardised incidence of both treatment-attributable infections and laboratory abnormalities. Infectious AEs per patient over 6 months for ECP (0.27) were lower than both etanercept (0.85) and infliximab (1.35) for the same period of follow up, and even lower in comparison with MMF (0.375), although this was over a relatively short 3-month follow-up period. Infusion of MSCs was also associated with a comparably low incidence of AEs attributable to infusions (0.087 per patient/8 months). Reporting of AEs per patient treated with basiliximab was not directly comparable due to the longer 12-month follow-up period. However, most infections occurred within 3–6 months following treatment.

No laboratory abnormalities were observed on either ECP, infliximab or basiliximab. The 2-month cumulative incidence of laboratory abnormalities was reported in the case of etanercept (76%), MMF (79.8/44%) and pentostatin (57%). However, those events are reported regardless of attribution to the drug, and it is not possible to assess the extent to which these incidences are attributable to the treatment or not.

ECP treatment reported the lowest average number of severe AEs per patient (0.12) in comparison with imatinib (0.59) at a low dosage, pentostatin (0.69) and MMF (1.09) over a follow-up period of 3 months. Rituximab has only long-term results reported at 12 and 19.5 months of follow up in two studies within a US population. However, results of rituximab treatment have a lower number of AEs per patient in two separate studies reporting on an Asian population (0.14 and 0.19 *versus* 0.43 per patient/year). However, in general, pharmacological treatments were associated with a higher observed incidence of severe AEs when compared with ECP treatment.

Whilst this review focussed specifically on AEs associated with second- and third-line management of GvHD, in clinical practice harms are balanced with potential benefits. Our findings are in line with United Kingdom (UK) and US

guidelines that support the harm–benefit profile of ECP when used in the management of aGvHD.[12,14] The studies included in this review show that, for both acute and chronic GvHD, ECP treatment has specific episodes of hypotension during apheresis, but they are usually asymptomatic, and laboratory anomalies were rare and mostly transient in nature.[27,41,42]

The evidence base quantifying AEs of interventions and therapeutics for second- and third-line treatment of aGvHD and cGvHD after allo-HSCT is limited.[63,64] This systematic review of both second- and third-line treatments was designed to identify the available information in the published literature regarding aGvHD and cGvHD after allo-HSCT but does have some limitations. Being descriptive, the results presented in this review, whilst standardised, do not adjust for patient, disease or treatment factors that differ between the various populations described in the included studies that may also influence the risk of AEs. In particular, none of these descriptive comparisons were adjusted for pre-treatment with steroids. Whilst corticosteroids were out of scope of this review, the observed rates of infections on the various second-line therapies reviewed may be influenced by the duration and dosage of any prior first-line steroid management of GvHD. In addition, it could not be fully ascertained from all included studies whether patients were being treated with any of the study therapies as monotherapy or in combination. This may limit this review's capacity to attribute any observed differences in AE rate to any one treatment. The lack of data around disease severity also makes it difficult to separate any of the observed differences in clinical outcome by therapy from variations in baseline disease severity. Furthermore, the full range of available therapies for GvHD after allo-HSCT was not captured in the included articles satisfying the inclusion criteria for this review. There was some variability in the grading of AEs across included studies. A formal meta-analysis sourcing individual patient data or key confounder aggregate data would be required to better separate treatment effects from these important sources of potential confounding. Finally, whilst the scope of this review was limited to AE reporting only, the harm profile of the therapies analysed needs to be balanced with their respective benefits for informed decision making in the clinical management of GvHD. Therapeutic burden, whilst outside the scope for our review, is also an important consideration in treatment selection. This is relevant for ECP, which requires central line placement and ongoing maintenance in addition to frequent clinic visits.

Overall, the reported incidence of infectious AEs in aGvHD and severe AEs in cGvHD was lower compared with pharmaceutical-only management. Formal statistical comparisons, including adjustment for corticosteroid pre-treatment, severity of GvHD and patient cohort heterogeneity, would be required to establish whether these observed reductions can be attributable to ECP itself.

## Author contributions

VV designed the study, ran the analysis, reviewed and interpreted the results and drafted and reviewed the manuscript.

EM designed the study, reviewed and interpreted the results and reviewed the manuscript.

RZ designed the study, reviewed and interpreted the results and reviewed the manuscript.

TS designed the study, reviewed and interpreted the results and drafted and reviewed the manuscript.

## Conflict of interest statement

VV, EM, RZ, and TS are/were employees of Synergus AB – health economics and market access consulting company, which received a grant from Mallinckrodt Pharmaceuticals to perform the study. Mallinckrodt reviewed the manuscript only to verify accuracy of product mentions.

## Ethical/consent statement

Our study did not require an ethical board approval because is was a systematic review of already published studies, each of which had obtained their own individual approval.

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## Supplemental material

Supplemental material for this article is available online.

## References


1. Holtick U, Albrecht M, Chemnitz JM, *et al.* Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation for haematological malignancies in adults. *Cochrane Database Syst Rev* 2014; 4: CD010189.
2. Müller LP and Müller-Tidow C. The indications for allogeneic stem cell transplantation in myeloid malignancies. *Dtsch Arztebl Int* 2015; 112: 262–270.
3. Passweg JR, Baldomero H, Bader P, *et al.* Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplant* 2017; 52: 811–817.
4. Flowers ME, Parker PM, Johnston LJ, *et al.* Comparison of chronic graft-versus-host disease after transplantation of peripheral blood stem cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. *Blood* 2002; 100: 415–419.
5. Zecca M, Prete A, Rondelli R, *et al.* Chronic graft-versus-host disease in children: incidence, risk factors, and impact on outcome. *Blood* 2002; 100: 1192–1200.
6. Wingard JR, Majhail NS, Brazauskas R, *et al.* Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J Clin Oncol* 2011; 29: 2230–2239.
7. Paczesny S, Hakim FT, Pidala J, *et al.* National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: III. The 2014 Biomarker Working Group Report. *Biol Blood Marrow Transplant* 2015; 21: 780–792.
8. Arai S, Arora M, Wang T, *et al.* Increasing incidence of chronic graft-versus-host disease in allogeneic transplantation: a report from the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant* 2015; 21: 266–274.
9. Hart JW, Shiue LH, Shpall EJ, *et al.* Extracorporeal photopheresis in the treatment of graft-versus-host disease: evidence and opinion. *Ther Adv Hematol* 2013; 4: 320–334.
10. MacMillan ML, Weisdorf DJ, Wagner JE, *et al.* Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: comparison of grading systems. *Biol Blood Marrow Transplant* 2002; 8: 387–394.
11. Weisdorf D, Haake R, Blazar B, *et al.* Treatment of moderate/severe acute graft-versus-host disease after allogeneic bone marrow transplantation: an analysis of clinical risk features and outcome. *Blood* 1990; 75: 1024–1030.
12. Dignan FL, Clark A, Amrolia P, *et al.* Diagnosis and management of acute graft-versus-host disease. *Br J Haematol* 2012; 158: 30–45.
13. Dignan FL, Amrolia P, Clark A, *et al.* Diagnosis and management of chronic graft-versus-host disease. *Br J Haematol* 2012; 158: 46–61.
14. Martin PJ, Rizzo JD, Wingard JR, *et al.* First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant* 2012; 18: 1150–1163.
15. Rizk M, Monaghan M, Shorr R, *et al.* Heterogeneity in studies of mesenchymal stromal cells to treat or prevent graft-versus-host disease: a scoping review of the evidence. *Biol Blood Marrow Transplant* 2016; 22: 1416–1423.
16. Allison TL. Immunosuppressive therapy in transplantation. *Nurs Clin North Am* 2016; 51: 107–120.
17. Sarantopoulos S, Cardones AR and Sullivan KM. How I treat refractory chronic graft-versus-host disease. *Blood* 2019; 133: 1191–1200.
18. Escamilla Gómez V, García-Gutiérrez V, Caballero-Velázquez T, *et al.* Ruxolitinib in refractory acute and chronic graft-versus-host disease: a multi-center survey study. *Bone Marrow Transplant*. Epub ahead of print 7 November 2019. DOI: 10.1038/s41409-019-0731-x.
19. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; 62: 1006–1012
20. Zorzela L, Loke YK, Ioannidis JP, *et al.* PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 2016; 352: i157.
21. Cooper H, Hedges LV and Valentine JC. (eds). *The handbook of research synthesis and meta-analysis*. 2nd ed. New York: Russell Sage Foundation, 2009.
22. Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1–12.

23. Santaguida P. The development of the McHarm quality assessment scale for adverse events: delphi consensus on important criteria for evaluating harms. http://hiru.mcmaster.ca/epc/mcharm.pdf (accessed December 15, 2017).
24. National Cancer Institute's. Common toxicity criteria v3.0. 2006. https://www.eortc.be/services/doc/ctc/ (accessed December 15 2017).
25. World Health Organization. WHO toxicity grading scale for determining the severity of adverse events. https://www.fda.gov/media/73679/download (accessed December 15 2017).
26. Khandelwal P, Emoto C, Fukuda T, *et al.* A prospective study of alemtuzumab as a second-line agent for steroid-refractory acute graft-versus-host disease in pediatric and young adult allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2016; 22: 2220–2225.
27. Calore E, Calo A, Tridello G, *et al.* Extracorporeal photochemotherapy may improve outcome in children with acute GVHD. *Bone Marrow Transplant* 2008; 42: 421–425.
28. Gatza E, Braun T, Levine JE, *et al.* Etanercept plus topical corticosteroids as initial therapy for grade one acute graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2014; 20: 1426–1434.
29. Levine JE, Paczesny S, Mineishi S, *et al.* Etanercept plus methylprednisolone as initial therapy for acute graft-versus-host disease. *Blood* 2008; 111: 2470–2475.
30. Alousi AM, Weisdorf DJ, Logan BR, *et al.* Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network. *Blood* 2009; 114: 511–517.
31. Couriel DR, Saliba R, de Lima M, *et al.* A phase III study of infliximab and corticosteroids for the initial treatment of acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2009; 15: 1555–1562.
32. Bolanos-Meade J, Logan BR, Alousi AM, *et al.* Phase 3 clinical trial of steroids/mycophenolate mofetil vs steroids/placebo as therapy for acute GVHD: BMT CTN.0802 *Blood* 2014; 124: 3221–3227; quiz.3335.
33. Jacobson PA, Huang J, Wu J, *et al.* Mycophenolate pharmacokinetics and association with response to acute graft-versus-host disease treatment from the Blood and Marrow Transplant Clinical Trials Network. *Biol Blood Marrow Transplant* 2010; 16: 421–429.
34. Xhaard A, Rocha V, Bueno B, *et al.* Steroid-refractory acute GVHD: lack of long-term improved survival using new generation anticytokine treatment. *Biol Blood Marrow Transplant* 2012; 18: 406–413.
35. Te Boome LC, Mansilla C, van der Wagen LE, *et al.* Biomarker profiling of steroid-resistant acute GVHD in patients after infusion of mesenchymal stromal cells. *Leukemia* 2015; 29: 1839–1846.
36. Zhao K, Lou R, Huang F, *et al.* Immunomodulation effects of mesenchymal stromal cells on acute graft-versus-host disease after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2015; 21: 97–104.
37. Baygan A, Aronsson-Kurttila W, Moretti G, *et al.* Safety and side effects of using placenta-derived decidual stromal cells for graft-versus-host disease and hemorrhagic cystitis. *Front Immunol* 2017; 8: 795.
38. Kebriaei P, Isola L, Bahceci E, *et al.* Adult human mesenchymal stem cells added to corticosteroid therapy for the treatment of acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2009; 15: 804–811.
39. Schmidt-Hieber M, Fietz T, Knauf W, *et al.* Efficacy of the interleukin-2 receptor antagonist basiliximab in steroid-refractory acute graft-versus-host disease. *Br J Haematol* 2005; 130: 568–574.
40. Nikiforow S, Kim HT, Bindra B, *et al.* Phase I study of alemtuzumab for therapy of steroid-refractory chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2013; 19: 804–811.
41. Flowers M, Apperley J, Besien K, *et al.* A multicentre prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood* 2008; 112: 2667–2674.
42. Greinix H, Besien K, Elmaagacli A, *et al.* Progressive improvement in cutaneous and extracutaneous chronic graft-versus-host disease after a 24-week course of extracorporeal photopheresis–results of a crossover randomized study. *Biol Blood Marrow Transplant* 2011; 17: 1775–1782.
43. Baird K, Comis LE, Joe GO, *et al.* Imatinib mesylate for the treatment of steroid-refractory sclerotic-type cutaneous chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2015; 21: 1083–1090.

44. Chen GL, Arai S, Flowers ME, *et al.* A phase 1 study of imatinib for corticosteroid-dependent/refractory chronic graft-versus-host disease: response does not correlate with anti-PDGFRA antibodies. *Blood* 2011; 118: 4070–4078.

45. Arai S, Pidala J, Pusic I, *et al.* A randomized phase II study of imatinib and rituximab for cutaneous sclerosis after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2015; 21: S324.

46. Olivieri A, Locatelli F, Zecca M, *et al.* Imatinib for refractory chronic graft-versus-host disease with fibrotic features. *Blood* 2009; 114: 709–718.

47. Olivieri A, Cimminiello M, Corradini P, *et al.* Long-term outcome and prospective validation of NIH response criteria in 39 patients receiving imatinib for steroid-refractory chronic GVHD. *Blood* 2013; 122: 4111–4118.

48. Martin P, Storer B, Rowley S, *et al.* Evaluation of mycophenolate mofetil for initial treatment of chronic graft-versus-host disease. *Blood* 2009; 113: 5074–5082.

49. Jurado M, De La Mata C, Ruiz-Garcia A, *et al.* Adipose tissue-derived mesenchymal stromal cells as part of therapy for chronic graft-versus-host disease: a phase I/II study. *Cytotherapy* 2017; 19: 927–936.

50. Jacobsohn DA, Chen AR, Zahurak M, *et al.* Phase II study of pentostatin in patients with corticosteroid-refractory chronic graft-versus-host disease. *J Clin Oncol* 2007; 25: 4255–4261

51. Jacobsohn DA, Gilman AL, Rademaker A, *et al.* Evaluation of pentostatin in corticosteroid-refractory chronic graft-versus-host disease in children: a Pediatric Blood and Marrow Transplant Consortium study. *Blood* 2009; 114: 4354–4360.

52. Malard F, Labopin M, Yakoub-Agha I, *et al.* Rituximab-based first line treatment for chronic GVHD after allogeneic SCT: results of a phase 2 study. *Blood*. Epub ahead of print 1 September.2017 DOI: 10.1182/blood-2017-05-786137.

53. Cutler C, Miklos D, Kim HT, *et al.* Rituximab for steroid-refractory chronic graft-versus-host disease. *Blood* 2006; 108: 756–762.

54. Kim SJ, Lee JW, Jung CW, *et al.* Weekly rituximab followed by monthly rituximab treatment for steroid-refractory chronic graft-versus-host disease: results from a prospective, multicentre, phase II study. *Haematologica* 2010; 95: 1935–1942.

55. Teshima T, Nagafuji K, Henzan H, *et al.* Rituximab for the treatment of corticosteroid-refractory chronic graft-versus-host disease. *Int J Hematol* 2009; 90: 253–260.

56. Johnston LJ, Brown J, Shizuru JA, *et al.* Rapamycin (sirolimus) for treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2005; 11: 47–55.

57. Messina C, Locatelli F, Lanino E, *et al.* Extracorporeal photochemotherapy for paediatric patients with graft-versus-host disease after haematopoietic stem cell transplantation. *Br J Hematol* 2003; 122: 118–127.

58. Basara N, Blau WI, Kiehl MG, *et al.* Efficacy and safety of mycophenolate mofetil for the treatment of acute and chronic GVHD in bone marrow transplant recipient. *Transplant Proc* 1998; 30: 4087–4089.

59. Herrmann R, Sturm M, Shaw K, *et al.* Mesenchymal stromal cell therapy for steroid-refractory acute and chronic graft versus host disease: a phase 1 study. *Int J Hematol* 2012; 95: 182–188.

60. Socié G, Vigouroux S, Yakoub-Agha I, *et al.* A phase 3 randomized trial comparing inolimomab vs usual care in steroid-resistant acute GVHD. *Blood* 2017; 129: 643–649.

61. Arai S, Pidala J, Pusic I, *et al.* A randomized phase II crossover study of imatinib or rituximab for cutaneous sclerosis after hematopoietic cell transplantation. *Clin Cancer Res* 2016; 22: 319–327.

62. Basara N and Blau W. The efficacy and safety of mycophenolate mofetil (MMF) in the treatment of acute and chronic GVHD in bone marrow transplant patients. *Bone Marrow Transplant* 1998; 21(Suppl. 1): S117.

63. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965; 58: 295–300.

64. Tantikul C, Dhana N, Jongjarearnprasert K, *et al.* The utility of the World Health Organization-the Uppsala Monitoring Centre (WHO-UMC) system for the assessment of adverse drug reactions in hospitalized children. *Asian Pac J Allergy Immunol* 2008; 26: 77–82.