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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

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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 assess 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

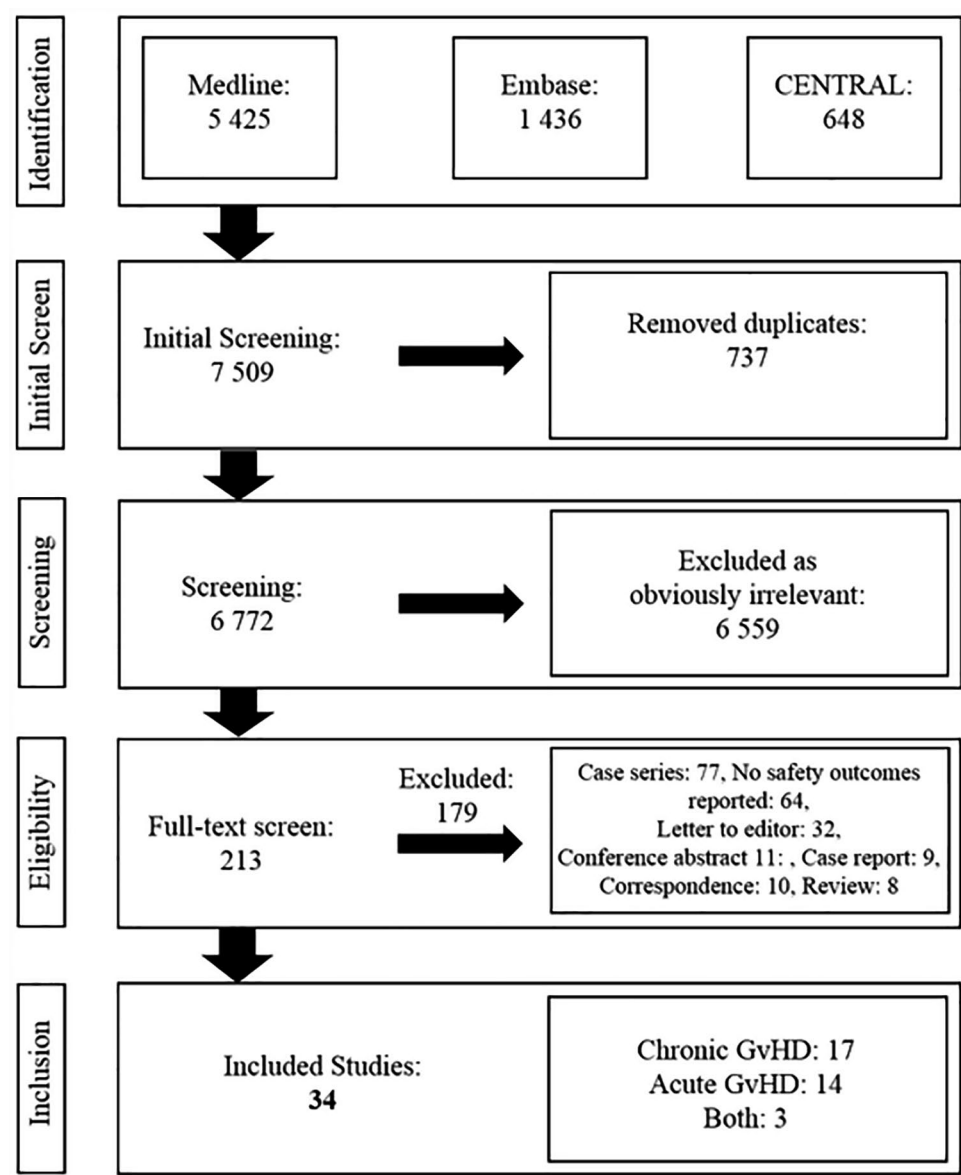


Figure 1. PRISMA flow chart of articles included in this systematic review. CENTRAL, Cochrane central register of controlled trials; GvHD, graft-versus-host disease; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCTs, randomised controlled trials.

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 (200mg) 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	Khandetwal <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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
MSC	Xhaard <i>et al.</i> ³⁴	France	1999–2010	Cohort study	Retrospective	93	52	Mix	1–4	30 (5–58)	60	No	No	No	n.r.
	Boome <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> ³⁷	Sweden	2011–2014	Cohort study	Retrospective	44	34	Mix	2–4	49 (1–68)	58.8	Yes	Yes	No	Non-industry funders
	Kebriaei <i>et al.</i> ³⁸	US	2005–2006	Clinical trial	Prospective	31	31	Adult	2–4	52 (34–67)	67.7	No	No	No	Industry funder
Pentostatin	Alousi <i>et al.</i> 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 <i>et al.</i> 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															
Alentuzumab	Nikiforow <i>et al.</i> 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 <i>et al.</i> ⁴¹	International	2002–2005	RCT, phase II	Prospective	95	48	Mix	n.r.	41 (16–67)	59	No	Yes	No	Industry funder
	Greinix <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> ⁴⁸	US	2004–2008	RCT	Prospective	157	74	Mix	n.r.	n.r.	55	No	Yes	No	Industry and non-industry funders
MSC	Jurado <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 of interest	Population	GvHD grade	Age (range)	Male (%)	Harm outcome as primary objective	Harm outcomes defined	Grading system applied	Funding source
Rituximab	Malard <i>et al.</i> ⁵²	France	2008–2012	Multicentre, phase II trial	Prospective	24	Adult	0–3	47 (23–63)	71	No	No	No	Industry non-industry funders
	Cutler <i>et al.</i> ⁵³	US	2004–2005	Open-label, phase I/II study	Prospective	21	Adult	0–4	42 (21–62)	48	No	Yes	Yes, CTC NCI	Industry non-industry funders
	Kim <i>et al.</i> ⁵⁴	Korea	n.r.	Multicentre, open label, phase II trial	Prospective	37	Mix	n.r.	29 (8–57)	54.1	No	No	Yes, n.r.	n.r.
	Teshima <i>et al.</i> ⁵⁵	Japan	2006–2007	Open-label phase II study	Prospective	7	Adult	1–2	48 (24–55)	71	Yes	Yes	Yes, CTC NCI v3	Non-industry funder
	Arai <i>et al.</i> ⁴⁵	US	2011–2014	RCT crossover design	Prospective	72	Adult	n.r.	56 (21–78)	59	No	No	Yes, n.r.	Industry funders
Sirolimus	Johnston <i>et al.</i> ⁵⁶	US	n.r.	Clinical trial, phase II	Prospective	19	Adult	n.r.	41 (23–57)	n.r.	No	Yes	Yes, CTC NCI	Non-industry funders
Mixed aGvHD/cGvHD														
ECP	Messina <i>et al.</i> ⁵⁷	Italy	1992–2000	Cohort study	Retrospective	77	Paediatric	2–4	8.9 (0.3–20.5)	72.7	Yes	Yes	No	Non-industry funders
MMF	Basara <i>et al.</i> ⁵⁸	Germany	n.r.	Cohort study	Prospective	51	n.r.	1–4	n.r.	n.r.	Yes	Yes	No	n.r.
MSC	Hermann <i>et al.</i> ⁵⁹	Australia	2007–2010	Phase I trial	Prospective	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 <i>et al.</i> 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.	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	Most common AEs related to alemtuzumab reported.		1.733/6 months	
	Laboratory abnormalities			12			0.800/6 months	
ECP								
Calore <i>et al.</i> 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.	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	Average duration 180–240min. Causal relation of treatment with AEs not reported.	n.r.	0.067/6 months	
Etanercept								
Gatza <i>et al.</i> 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	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	Causal relation of treatment with AEs not reported.		0.029/6 months	
	Viral			18			0.529/6 months	
Levine <i>et al.</i> ²⁹	Bacterial	3 months	61	64	0.4 mg/kg (maximum dose 25 mg) twice weekly for 8 weeks.	n.r.	1.049/3 months	
	Fungal			17	Subcutaneous injection. Causal relation of treatment with AEs not reported.		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 <i>et al.</i> 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).	47%	–	
	Laboratory abnormalities	2 months		–	Subcutaneous injection twice weekly for 4 weeks All grade 3–5 toxicities are reported regardless of attribution to drug	76%	–	
Infliximab								
Couriel <i>et al.</i> 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 <i>et al.</i> ⁴⁰	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 <i>et al.</i> 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 <i>et al.</i> ³⁵	Serious AEs	12 months	50	75	1–2 × 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 <i>et al.</i> ³⁶	Bacterial	12 months	28	5	1–2 × 10 ⁶ cells/kg bodyweight	n.r.	0.178	
	Fungal			0	Infusion once a week until CR was reached, or until 8 doses had been administered.		0	
	Viral			4			0.143	
	Mixed infection			5			0.178	
Baygan <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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)	n.r.	0.094/3 months	
	Fungal			1	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.	0.031/3 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
Pentostatin								
Alousi <i>et al.</i> ³⁰	Infections Laboratory abnormalities	Nine months 2 months	45	-	Twice daily orally or intravenously All grade 3-5 adverse events are reported regardless of attribution to drug	80% 44%	- -	
Basiliximab								
Alousi <i>et al.</i> ³⁰	Infections Laboratory abnormalities	9 months 2 months	42	-	20mg/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% 57%	- -	Number of patients: 42 Grade 3-5 CI of infection: 67%/9 months Grade 3-5 CI of LA: 57%/2 months
Schmidt-Hieber <i>et al.</i> ³⁹	Bacterial Fungal Viral Laboratory abnormalities	12 months	23	10 2 5 0	20mg on days 1 and 4. The solution was administered over a period of 30min without premedication. Toxicity connected to treatment. Fungal infections accessed as proven or possible according to EORTC criteria.	n.r. n.r. n.r. n.r.	0.435 0.087 0.217 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 <i>versus</i> 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 <i>et al.</i> ⁶¹	Bacterial	12 months	13	Three times during week, 1 once a week for 3 weeks after.	0.462	Number of patients: 13 AE severity grade 3–5 per patient: 1.155/year
	Viral			Three dose levels: 3mg, 10mg, maximum 30mg.	0.385	
	Hematologic				0.308	
ECP						
Flowers <i>et al.</i> 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 <i>et al.</i> ⁴²	Mainly infections and vascular access problem	3 months	29	n.r.	0.10	
Imatinib						
Olivieri <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> ⁴³	Mostly laboratory abnormalities and gastrointestinal AEs	6 months	20	Adverse events - dose related Final dose of 100–300 mg daily	0.9	
Chen <i>et al.</i> 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 0.4–200 mg	
Arai <i>et al.</i> ⁴⁵	Mostly infections and laboratory abnormalities	19.5 months	35	200 mg daily	0.54	
MSC						
Herrmann <i>et al.</i> 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 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 <i>et al.</i> ⁴⁹	Mostly laboratory abnormalities, hematologic and infectious AEs	12 months	14	Group A: 1×10^6 /kg MSC Group B: 3×10^6 /kg MSC	0.214 0.500	
MMF						
Martin <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> ⁵¹	Mostly infections	6 months	51		0.69	
Rituximab						
Malard <i>et al.</i> 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 <i>et al.</i> ⁵³	Mostly infections	12 months	21		0.43	
Kim <i>et al.</i> ⁵⁴	Infections only	12 months	37		0.19	
Teshima <i>et al.</i> ⁵⁵	Infections only	12 months	7		0.14	
Arai <i>et al.</i> ⁴⁵	Mostly laboratory abnormalities and infections	19.5 months	37		0.46	
Sirrolimus						
Johnston <i>et al.</i> 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 it 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.

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