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Fisher SA, Cutler A, Doree C, Brunskill SJ, Stanworth SJ, Navarrete C, Girdlestone J

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[Intervention Review]

Mesenchymal stromal cells as treatment or prophylaxis for acute or chronic graft-versus-host disease in haematopoietic stem cell transplant (HSCT) recipients with a haematological condition

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ABSTRACT

Background

Recipients of allogeneic haematopoietic stem cell transplants (HSCT) can develop acute or chronic, or both forms of graft-versus-host disease (a/cGvHD), whereby immune cells of the donor attack host tissues. Steroids are the primary treatment, but patients with severe, refractory disease have limited options and a poor prognosis. Mesenchymal stromal cells (MSCs) exhibit immunosuppressive properties and are being tested in clinical trials for their safety and efficacy in treating many immune-mediated disorders. GvHD is one of the first areas in which MSCs were clinically applied, and it is important that the accumulating evidence is systematically reviewed to assess whether their use is favoured.

Objectives

To determine the evidence for the safety and efficacy of MSCs for treating immune-mediated inflammation post-transplantation of haematopoietic stem cells.

Search methods

We searched for randomised controlled trials (RCTs) in the Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library 2018, Issue 12), MEDLINE (from 1946), Embase (from 1974), CINAHL (from 1937), Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (from 1990) and ongoing trial databases to 6 December 2018. No constraints were placed on language or publication status.

Selection criteria

We included RCTs of participants with a haematological condition who have undergone an HSCT as treatment for their condition and were randomised to MSCs (intervention arm) or no MSCs (comparator arm), to prevent or treat GvHD. We also included RCTs which compared different doses of MSCs or MSCs of different sources (e.g. bone marrow versus cord). We included MSCs co-transplanted with haematopoietic stem cells as well as MSCs administered post-transplantation of haematopoietic stem cells.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

We employed a random-effects model for all analyses due to expected clinical heterogeneity arising from differences in participant characteristics and interventions.

Main results

We identified 12 completed RCTs (879 participants), and 13 ongoing trials (1532 enrolled participants planned). Of 12 completed trials, 10 compared MSCs versus no MSCs and two compared different doses of MSCs. One trial was in people with thalassaemia major, the remaining trials were for haematological malignancies. Seven trials administered MSCs to prevent GvHD, whereas five trials gave MSCs to treat GvHD.

In the comparison of MSCs with no MSCs, cells were administered at a dose of between 10^5 and 10^7 cells/kg in either a single dose (six trials) or in multiple doses (four trials) over a period of three days to four months. The dose-comparison trials compared 2×10^6 cells/kg with 8×10^6 cells/kg in two infusions, or 1×10^6 cells/kg with 3×10^6 cells/kg in a single infusion.

The median duration of follow-up in seven trials which administered MSCs prophylactically ranged from 10 to 60 months. In three trials of MSCs as treatment for aGvHD, participants were followed up for 90 or 100 days. In two trials of MSCs as treatment for cGvHD, the mean duration of follow-up was 13.4 months (MSC group) and 23.6 months (control group) in one trial, and 56 weeks in the second trial. Five trials included adults only, six trials included adults and children, and one trial included children only. In eight trials which reported the gender distribution, the percentage of females ranged from 20% to 59% (median 35.8%).

The overall quality of the included studies was low: randomisation methods were poorly reported and several of the included studies were subject to a high risk of performance bias and reporting bias. One trial which started in 2008 has not been published and the progress of this trial is unknown, leading to potential publication bias. The quality of evidence was therefore low or very low for all outcomes due to a high risk of bias as well as imprecision due to the low number of overall participants, and in some cases evidence based on a single study. We found that MSCs may make little or no difference in the risk of all-cause mortality in either prophylactic trials (HR 0.85, 95% CI 0.50 to 1.42; participants = 301; studies = 5; $I^2 = 34\%$; low-quality evidence) or therapeutic trials (HR 1.12, 95% CI 0.80 to 1.56; participants = 244; studies = 1; very low-quality evidence), and no difference in the risk of relapse of malignant disease (prophylactic trials: RR 1.08, 95% CI 0.73 to 1.59; participants = 323; studies = 6; $I^2 = 0\%$; low-quality evidence) compared with no MSCs. MSCs were well-tolerated, no infusion-related toxicity or ectopic tissue formation was reported. No study reported health-related quality of life. In prophylactic trials, MSCs may reduce the risk of chronic GvHD (RR 0.66, 95% CI 0.49 to 0.89; participants = 283; studies = 6; $I^2 = 0\%$; low-quality evidence). This means that only 310 (95% CI 230 to 418) in every 1000 patients in the MSC arm are expected to develop chronic GvHD compared to 469 in the control arm. However, MSCs may make little or no difference to the risk of aGvHD (RR 0.86, 95% CI 0.63 to 1.17; participants = 247; studies = 6; $I^2 = 0\%$; low-quality evidence). In GvHD therapeutic trials, we are very uncertain whether MSCs improve complete response of either aGvHD (RR 1.16, 95% CI 0.79 to 1.70, participants = 260, studies = 1; very low-quality evidence) or cGvHD (RR 5.00, 95% CI 0.75 to 33.21, participants = 40, studies = 1; very low-quality evidence).

In two trials which compared different doses of MSCs, we found no evidence of any differences in outcomes.

Authors' conclusions

MSCs are an area of intense research activity, and an increasing number of trials have been undertaken or are planned. Despite a number of reports of positive outcomes from the use of MSCs for treating acute GvHD, the evidence to date from RCTs has not supported the conclusion that they are an effective therapy. There is low-quality evidence that MSCs may reduce the risk of cGvHD. New trial evidence will be incorporated into future updates of this review, which may better establish a role for MSCs in the prevention or treatment of GvHD.

PLAIN LANGUAGE SUMMARY

Mesenchymal stromal cells to treat or prevent graft-versus-host disease in stem cell transplant recipients

Review question

In people who receive a stem cell transplant for a haematological condition, can an additional infusion of mesenchymal stromal cells (MSCs) prevent the development of graft-versus-host disease (GvHD)? In people who have already developed GvHD as a result of their stem cell transplant, can MSCs improve their clinical outcome?

Background

Patients with leukaemia or other blood disorders may be treated with blood stem cells from another person, but the immune cells in the graft can attack their tissues in a serious complication referred to as graft-versus-host disease (GvHD). Steroids are the standard treatment for GvHD, but if they are unable to stop the damage then treatment options are limited. In order to look for potential new treatments, a number of hospitals around the world have investigated the use of MSCs for inhibiting GvHD. MSCs are a type of cell that can develop into connective tissue (e.g. bone or cartilage), but they have also been found to have anti-inflammatory properties. For clinical trials, MSCs have

been isolated from different tissue sources (e.g. bone marrow, fat, or umbilical cords) and then grown in large numbers in the laboratory. The MSC preparations are then injected intravenously into the patient at the time they have their stem cell transplant or afterward, either to prevent GvHD (prophylaxis) or to treat ongoing disease. For patients being treated for GvHD, is treatment with MSCs safe and effective against complications of inflammation associated with GvHD?

Study characteristics

The evidence is current to 6 December 2018. We identified 12 studies and 13 ongoing trials. Ten studies compared MSCs with a control group, and two studies compared different doses of MSCs. Five trials included only adults, whereas six trials include both adults and children and one trial was exclusively performed in children. Of the 12 completed trials, one trial was in people with inherited blood disorders (thalassaemia major), and 11 trials were in people with blood cancers. In seven trials, MSCs were given to prevent GvHD, whereas in five trials, MSCs were given to people who had already developed GvHD. MSCs were derived from umbilical cord in two trials, bone marrow in seven trials and adipose tissue in one trial; in two trials the origin of MSCs was unknown. In the comparison of MSCs with no MSCs, cells were administered at a dose of between 10^5 and 10^7 cells/kg. Seven trials gave MSCs in a single dose, whereas five trials gave multiple doses of MSCs. Trial participants were followed up for between 10 and 60 months, or in those who had already developed GvHD, up to two years. Three trials were funded and carried out by a commercial manufacturer, using their cultured mesenchymal stromal cells known as Prochymal. All trials included both men and women.

Key results

MSCs may have little or no difference in the risk of death or relapse of malignant disease, in either GvHD prevention or treatment trials, as the quality of evidence was low. MSCs were well-tolerated, no infusion-related toxicity or ectopic tissue formation was reported. No study reported health-related quality-of-life. In trials where MSCs were administered to prevent GvHD, MSCs may reduce the risk of developing chronic GvHD, but may make little or no difference to the risk of developing acute GvHD. In GvHD treatment trials, we are very uncertain whether MSCs improve complete response of either acute or chronic GvHD as the quality of evidence is very low. We found no differences in outcomes between participants who received a higher dose of MSCs when compared with those who received a lower dose of MSCs.

Quality of the evidence

The quality of evidence is low or very low for all outcome measures, due to the small number of trials and low number of study participants included in this review. One trial started in 2008, but its results are unknown as it is not yet published. It is therefore difficult to draw conclusions or provide recommendations on the use of MSCs, either to prevent or treat GvHD. More trials with large numbers of study participants are needed to improve the quality of evidence.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. MSCs compared to control/placebo for treating immune-mediated inflammation post-transplantation and in autoimmunity

MSCs compared to control/placebo for treating immune-mediated inflammation post-transplantation and in autoimmunity

Patient or population: patients with a haematological condition who receive a haematopoietic stem cell transplant as treatment for their condition.

Settings: hospital

Intervention: MSCs

Comparison: No MSCs (control or placebo)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	control/placebo	MSCs				
All-cause mortality (prophylactic trials) (over duration of trial)	Study population		HR 0.85 (0.50 to 1.42)***	301 (5 studies)	⊕⊕⊕⊕ low ^{1,2}	
	374 per 1000**	326 per 1000** (232 to 460)				
All-cause mortality (therapeutic trials) (over duration of trial)	Study population		HR 1.12 (0.80 to 1.56)	244 (1 study)	⊕⊕⊕⊕ very low ^{1,3}	
	420 per 1000**	344 per 1000** (248 to 479)				
Safety of MSC infusion	See comment	See comment	Not estimable	334 (7 studies)	See comment	MSCs were well-tolerated, no infusion-related toxicity or ectopic tissue formation was reported in any study.
Health-related quality of life	Not estimable	Not estimable	Not estimable	(no studies)	-	Outcome not reported.
Relapse of malignant disease (prophylactic trials)	99 per 1000	107 per 1000 (35 to 185)	RR 1.08 (0.73 to 1.59)	323 (6 studies)	⊕⊕⊕⊕ low ^{1,2}	

(>12-month follow-up)					
Incidence of acute GvHD (prophylactic trials)	Study population		RR 0.86	247	⊕⊕○○
	391 per 1000	336 per 1000 (246 to 457)	(0.63 to 1.17)	(6 studies)	low ^{1,2}
Incidence of chronic GvHD (prophylactic trials)	Study population		RR 0.66	283	⊕⊕○○
	469 per 1000	310 per 1000 (230 to 418)	(0.49 to 0.89)	(6 studies)	low ^{1,2}
Acute GvHD complete response (therapeutic trials)	Study population		RR 1.16	260	⊕○○○
	299 per 1000	347 per 1000 (236 to 508)	(0.79 to 1.70)	(1 study)	very low ^{1,3}
Chronic GvHD complete response (therapeutic trials)	Study population		RR 5.00	40	⊕○○○
	100 per 1000	500 per 1000 (75 to 1000)	(0.75 to 33.21)	(1 study)	very low ^{1,3}

*The basis for the **assumed risk** is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; GvHD: graft-versus-host disease; HR: hazard ratio; RR: Risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded by 1 for high risk of bias due to inclusion of trials that do not report methods of random sequence generation or allocation, are unblinded, or are subject to selective reporting.

² Downgraded by 1 for imprecision as the total population size is less than 400 participants.

³ Downgraded by 2 for imprecision as the total population size is less than 400 participants and evidence is based on only one study.

*The assumed risk is based on the observed rate in controls.

**The hazard ratio for all-cause mortality has been converted to a relative risk to estimate the corresponding risk in the MSC group.

*** A hazard ratio less than 1 indicates advantage to MSCs, a value greater than 1 indicates advantage to no MSCs.

BACKGROUND

Description of the condition

Graft-versus-host disease (GvHD) is a potentially life-threatening complication of allogeneic haematopoietic stem cell transplantation (HSCT) used as a treatment for patients with haematological malignancies, severe aplastic anaemia and rare inherited genetic abnormalities. GvHD arises when donor immune cells that are contained within or differentiate from the stem cell transplant 'attack' host tissues, in effect rejecting the host as a foreign entity. Multiple organs are involved with the liver, skin and gastrointestinal tract being particularly affected. Acute GvHD (aGvHD) is a common complication and up to 80% of HSCT recipients can develop varying degrees of disease. Severity of disease is graded from I to IV depending on the extent of involvement of the three target organs. Between 50% and 80% of patients respond to standard first-line therapies based on steroids. Patients who do not respond have a poor outlook and the five-year survival of severe acute or steroid-refractory GvHD patients is between 5% and 25% (Martin 1990; Van Lint 1998). Current second-line therapies used after failure of steroid treatment are numerous, but have shown little efficacy in reducing death. Recent studies have started to suggest that mesenchymal stromal cells (MSCs) may be effective as a second-line therapy, with a reported response in up to 50% of patients (Le Blanc 2008).

Chronic GvHD (cGvHD) is immunologically distinct from aGvHD and generally manifests after 100 days post-transplant (Flowers 2015; Socié 2014). The recorded incidence of cGvHD has risen over the last few decades, a trend ascribed to the transplantation of older patients and the increased use of peripheral blood stem cells as compared to bone marrow. Acute GvHD is a prominent risk factor for cGvHD, and therefore the prevention or amelioration of early immune complications is desirable.

In this review we wish to identify and appraise the complete current literature reporting on the outcome of randomised, controlled trials to determine whether MSC infusion is safe, can reduce inflammation induced by immune-mediated destruction of host tissues, and provide clinical benefit to patients where GvHD is a potential complication.

Description of the intervention

MSCs are increasingly being applied as an experimental cellular therapy for many different clinical indications. Identified originally in cultures of bone marrow, they may be derived from a number of tissues and are identified by a panel of cell surface markers, and their ability to differentiate into connective tissue elements: osteoblasts, chondrocytes, and adipocytes (Dominici 2006). Originally envisioned as a treatment for damaged bone and cartilage, the finding that MSCs possess immunosuppressive properties has focused their use on treating immune-mediated inflammation associated with transplantation of haematopoietic stem cells (Ringden 2011) or solid organs (English 2010), and autoimmune diseases (Dazzi 2011). At present, the prophylaxis and treatment of GvHD are amongst the applications of MSC for which clinical trials are the most advanced.

Bone marrow and adipose tissue are the main sources that have can be exploited for the generation of autologous MSCs. However, not all patients are able to donate sufficient material to generate

the required cell numbers within the time needed for treatment. Therefore, allogeneic MSCs have been used in many trials, without human leukocyte antigen (HLA) matching and with no apparent adverse outcomes as compared to autologous, and low rates of donor-specific anti-HLA antibody development (Hare 2012; Hare 2017). Increasingly, umbilical cord is being used as an allogeneic source of clinical-grade MSCs due to the ease of acquisition and expansion (Capelli 2015). While fetal calf serum has traditionally been used in MSC culture medium, platelet lysate is now accepted as a suitable source of non-xenogeneic growth factors (Capelli 2015).

MSCs generally are infused intravenously into patients in single or multiple doses. Relatively low numbers of cells are infused with doses based on weight (ranging from 0.4×10^6 to 9×10^6 cells / kg) in the case of therapy for GvHD. The timing of intervention varies between diseases and disease states. In general, MSC therapy appears to be safe with few reported adverse reactions (Lalu 2012). However, one study reported an increase in relapse rates upon treatment with MSCs (Ning 2008). In most cases MSCs are infused in addition to standard care and are compared with control groups that are treated with placebo and standard care or standard care alone.

How the intervention might work

MSCs produce growth factors to aid tissue regeneration (Caplan 2006) and have potent anti-inflammatory potential with the ability to suppress the activation and effector function of cells of the immune system. They appear to employ multiple mechanisms to suppress inflammation, utilising secreted factors (prostaglandins), enzymes (indoleamine 2,3-deoxygenase) and other agents to inhibit a number of immune cell types (Fibbe 2007). They reduce the proliferative capacity of naive and memory T-cells, B cells and effector function of $\gamma\delta$ T-cells, natural killer cells and neutrophils. They also modulate the function of cells that are able to induce potent immune responses, such as monocytes and dendritic cells.

In order for relatively low cell numbers to exert meaningful effects on strong immune activities such as GvHD, it has been thought that infused MSC accumulate at sites of inflammation and tissue damage, or draining lymph nodes (Leibacher 2016). The majority are found in the lung immediately after infusion, with some appearing later in the liver and spleen (Gholamrezaezhad 2011). There is also an argument that any action by MSC is mediated by their release of exosomes while they are trapped in the lungs, and there is increasing interest in using such microvesicles rather than whole cells as the therapeutic treatment (Rani 2015).

Why it is important to do this review

There is increasing interest in the use of MSCs in the clinic and numerous small non-randomised observational trials have already been completed. At present, the indications in which MSCs are used in most advanced clinical trials as a cellular therapy are the treatment of GvHD and Crohn's disease. There is a now a need to identify and appraise the randomised controlled trial (RCT) evidence robustly for effectiveness and safety.

The review will inform the wider clinical community as to the efficacy and safety of MSCs in their use as an anti-inflammatory cellular therapy, and highlight the areas where further evidence is required. Furthermore, it will inform health organisations as to

the cost-effectiveness of banking MSCs to provide an 'off the shelf' service for treatment of GvHD and other indications.

OBJECTIVES

To determine the evidence for the safety and efficacy of mesenchymal stromal cells (MSCs) for treating or preventing graft-versus-host disease (GvHD) post-transplantation of haematopoietic stem cells in patients with a haematological condition.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

All patients with a haematological condition who receive a haematopoietic stem cell transplant (HSCT) as treatment for their condition.

Types of interventions

Primary intervention: use of mesenchymal stromal cells (MSCs) as treatment or prophylaxis for acute or chronic graft-versus-host disease (aGvHD, cGvHD).

We considered the following groups of trials.

- Use of MSCs versus placebo or no MSC treatment
- Use of MSCs of type (e.g. number of doses or passages) or source (e.g. autologous versus allogeneic, or bone marrow versus cord) A versus MSC of type or source B.

We included MSCs co-transplanted with haematopoietic stem cells as well as MSCs administered post-transplantation of haematopoietic stem cells

Types of outcome measures

We considered outcomes common to all patient groups, as well as those relevant to either therapeutic or prophylactic trials.

Primary outcomes

- All-cause mortality
- Safety of MSC infusion – acute toxicity, ectopic tissue formation or oncogenesis

Secondary outcomes

All studies

- Health-related quality of life using validated scale
- Relapse of malignant disease
- Infection rates
- Engraftment

MSCs given for the prevention of GvHD

- Incidence of aGvHD
- Incidence of cGvHD

MSCs given as treatment for GvHD

- Complete response and partial response to aGvHD
- Complete response and partial response to cGvHD

Search methods for identification of studies

Electronic searches

The Systematic Review Initiative's (SRI) Information Specialist (CD) formulated the search strategies used in collaboration with the Cochrane Haematological Malignancies Group. We searched for randomised controlled trials (RCTs) in the following databases to 6 December 2018.

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, 2018, Issue 12) (www.cochranelibrary.com/) ([Appendix 1](#))
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, 1946 to present) ([Appendix 2](#))
- Embase (OvidSP, 1974 to present) ([Appendix 3](#))
- CINAHL (EbscoHost, 1937 to present) ([Appendix 4](#))
- PubMed (e-publications ahead of print only) (<http://www.ncbi.nlm.nih.gov/pubmed>) ([Appendix 5](#))
- LILACS (1980 to present) (<http://lilacs.bvsalud.org/en/>) ([Appendix 6](#))
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to present). ([Appendix 7](#)).

We searched for ongoing trials in the following clinical trial registers.

- ClinicalTrials.gov (<https://www.clinicaltrials.gov/>) ([Appendix 8](#))
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/>). ([Appendix 9](#))
- HKU Clinical Trials Registry (HKUCTR) (<http://www.hkuctr.com/>) ([Appendix 10](#)).

We combined searches in MEDLINE and Embase with adaptations of the recommended Cochrane RCT search filters as detailed in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Lefebvre 2011](#)) and the relevant Scottish Intercollegiate Guidelines Network (SIGN) systematic review filters (www.sign.ac.uk/methodology/filters.html). Searches in CINAHL were combined with the SIGN randomised controlled trial and systematic review filters. Searches were not limited by language, year of publication or publication type. Search strategies for all databases are presented in the appendices.

Eligible studies identified from searches to 10 October 2017 were incorporated into this review as included studies. Potential studies identified from the final search update prior to publication of this review (6 December 2018) were included as awaiting assessment and are denoted as such in [Characteristics of studies awaiting classification](#).

Searching other resources

We checked references of all identified trials, relevant review articles and current treatment guidelines for further literature. These searches were limited to the 'first generation' reference lists.

We attempted to contact the lead authors of ongoing trials which did not have an expected completion date or for which the completion date had passed but no publications had been identified. We also contacted the lead authors of relevant studies, study groups and international experts working in this field to identify any unpublished material, or to gather information regarding ongoing studies.

Data collection and analysis

Selection of studies

We selected studies according to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). One review author, Carolyn Doree (CD), initially screened all search hits for relevance against the eligibility criteria and discarded all those that were clearly irrelevant. Thereafter, two other review authors (JG and either AC or SF) independently screened all the remaining hits (titles and abstracts) for relevance against the full eligibility criteria. We retrieved full-text papers for all those references for which a decision of eligibility could not be made from title and abstract alone. We resolved differences of opinion through discussion and consensus. Studies which did not meet our eligibility criteria are detailed in the [Characteristics of excluded studies](#) table.

Data extraction and management

Two review authors (JG and either AC or SF) independently extracted data onto standardised forms. Disagreements were resolved through discussion and consensus. The review authors were not blinded to the names of authors, institutions, journals or the outcomes of the trials. We extracted the following data for each trial.

- Trial details: study citation(s), objectives, study design, location, setting, methods of treatment allocation, randomisation and blinding, inclusion and exclusion criteria, defined primary and secondary outcomes, length of follow-up, data stratification, stopping rules described, statistical analyses and funding.
- Characteristics of participants: age, gender, disease, disease class, number of randomised participants, number of analysed participants, exclusions or withdrawals, reasons for exclusions or withdrawals, protocol violations.
- Characteristics of HSCT: source of HSCT, conditioning regimen, GvHD prophylaxis.
- Interventions: source of intervention, dosage and timing of intervention, nature of comparator, additional interventions administered, any differences between interventions.
- Outcomes: all-cause mortality, safety of MSC infusion (acute toxicity, ectopic tissue formation, oncogenesis), adverse events, time to survival, health-related quality of life, relapse of malignant disease, infection rates, engraftment. In GvHD therapeutic trials: complete and partial response, alleviation of all organ involvement (GvHD). In GvHD prophylactic trials: incidence of aGvHD, incidence of cGvHD.

We emailed the authors of two publications arising from one trial (Kuzmina 2012) to request further information regarding possible patient overlap and sample size differences between the two publications, which the authors kindly provided. We also emailed the lead author of one study (Jurado 2017) to request clarity over some apparent data discrepancies regarding adverse events

contained in the published paper; the correct data were kindly provided.

Following data extraction, we assessed the quality of each included study by using the 'Risk of bias' tool in the Review Manager 5 software (RevMan 2011).

Assessment of risk of bias in included studies

Two review authors (SF and JG) independently assessed all included studies for possible risk of bias as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We assessed the design, conduct and analysis of the trial using a three-point scale: low risk of bias, high risk of bias or unclear. To assess risk of bias, we included the following questions in the 'Risk of bias' table for each included study.

- Selection bias: was the allocation sequence adequately generated? Was allocation adequately concealed?
- Performance bias: where possible, were the study participants and personnel adequately blinded?
- Detection bias: was blinding of the outcome assessors effective in preventing systematic differences in the way in which the outcomes were determined?
- Attrition bias: were incomplete outcome data adequately addressed for each outcome?
- Reporting bias: are reports of the study free of selective outcome reporting?
- Other sources of bias: was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

Where sufficient data were available, we performed quantitative assessments using Review Manager (RevMan 2011).

For dichotomous outcomes we recorded the number of events and the total number of participants in each treatment arm. We present dichotomous outcomes as pooled risk ratios (RR) with 95% confidence intervals (CI). For survival data we used hazard ratios (HR) to express the intervention effect.

Unit of analysis issues

We did not identify any cluster-randomised trials or cross-over studies eligible for inclusion in this review.

Dealing with missing data

We assumed missing data to be due to random effects. We recorded the number of patients lost to follow-up and excluded/withdrawn from each trial. If survival data were missing, we estimated log hazard ratios and standard errors using the methods from Parmar and Tierney (Parmar 1998; Tierney 2007). In two studies, individual patient survival data were presented, but in one study (Wu 2013), survival analysis was not performed and in the other study (Ning 2008), insufficient data were presented to use estimation methods. In these studies, survival models were fitted to reported data using Cox proportional hazards regression, implemented using the statistical R v2.14.1 to calculate hazard ratios. Our preferred analysis was by intention-to-treat (ITT), but where insufficient data were presented in the included studies, we performed per protocol analyses.

Assessment of heterogeneity

We assessed heterogeneity within selected studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 9 (Deeks 2011). We assessed statistical heterogeneity of treatment effects between trials by using a χ^2 test with a significance level at P value < 0.1 . We used the I^2 statistic to quantify the amount of possible heterogeneity (we considered an $I^2 > 30\%$ to indicate moderate heterogeneity and an $I^2 > 75\%$ to indicate considerable heterogeneity). We intended to explore potential causes of heterogeneity by sensitivity and subgroup analysis but this was prohibited by the low number of included studies.

If sufficient data are identified in future updates of this review, we will assess clinical heterogeneity based on the data extracted about the characteristics (e.g. by examining differences in study quality, in the donation history and donor characteristics, and in the definition or measurement of outcomes of each study) of the included studies.

Assessment of reporting biases

We believe that every effort has been made to identify unpublished studies. A formal assessment of publication bias using funnel plots was intended but was not possible due to the paucity of studies (It is acknowledged that asymmetry, of which publication bias is one cause, is difficult to detect with the small numbers of studies (i.e. fewer than 10) often encountered in systematic reviews).

Data synthesis

We undertook meta-analysis where we considered that studies were sufficiently homogeneous in terms of clinical setting and study design. Meta-analysis was performed using the Review Manager software (RevMan 2011). We used random-effects models throughout due to expected clinical heterogeneity due to differences in participant characteristics, cell doses and follow-up time points.

As well as quantitative synthesis, our overall interpretation of the data also incorporates insights from a qualitative summary. We have based our conclusions on patterns of results identified across clearly tabulated results of included studies as well as summary measures.

For disease relapse, we analysed data separately according to the duration of follow-up: short term (≤ 12 months) and long term (> 12 months).

We have used the GRADE profiler to create a 'Summary of findings' table as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 11 (Schünemann 2011). We focus on those outcomes which we consider to be most clinically relevant for this intervention, namely all-cause mortality, safety of MSC infusion, incidence of acute and chronic GvHD (prophylactic trials), and complete response to acute and chronic GvHD (therapeutic trials).

Subgroup analysis and investigation of heterogeneity

Where sufficient trials were identified, we intended to perform subgroup analyses according to the following criteria:

- participant (children versus adults);
- intervention (by type of MSC, e.g. number of doses or source);

- underlying disease (malignant versus non-malignant);
- MSC usage (prophylactic versus therapeutic) (mortality and response outcomes).

However, subgroup analyses were largely prohibited by the paucity of included studies. We only identified sufficient trials to perform subgroup analysis comparing malignant versus non-malignant disease (incidence of aGvHD) and prophylactic versus therapeutic trials (all-cause mortality). We will perform further subgroup analyses in future updates of the review if sufficient studies are identified.

Sensitivity analysis

We planned to assess the robustness of our findings through sensitivity analyses, however this was not feasible due to the limited number of studies included in meta-analyses. We will perform the following sensitivity analyses in future updates of the review if sufficient studies are identified:

- including only those trials at low risk of selection bias (trials assessed as low risk for random sequence generation and concealment of treatment allocation);
- including only those trials in which 25% participants or less were lost to follow-up;
- including only those trials which are published as full-text papers (i.e. excluding abstract-only publications and unpublished trials).

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#) and [Characteristics of ongoing studies](#).

Results of the search

See the PRISMA Flow Diagram (Figure 1). From searches carried out to 6 December 2018, we identified a total of 4601 records, comprising 3848 published papers or conference abstracts, and 753 ongoing trial records. We also identified four additional references resulting from subsequent detailed screening as follows. One published trial (Wu 2013) was identified through checking of reference lists of a relevant published systematic review (this trial was included in the initial search results but excluded on the basis of the abstract). Additionally, two commercially sponsored studies were published in abstract form only (Osiris Protocol 265; Osiris Protocol 280). We attempted to contact both Osiris Therapeutics Inc. and Mesoblast Ltd (who have acquired Osiris' stem cell unit since these trials were performed) by email with a request for further information on these trials, but no response was forthcoming. However, we identified an Australian Public Assessment Report and associated document relating to a submission to register Remestemcel-L (Prochymal) (subsequently withdrawn), which include detailed data relating to the trial described in Osiris Protocol 280. Permission to obtain these data was obtained from the Therapeutic Goods Administration, Australian Government subject to copyright (see Appendix 11). We also identified a press release relating to Osiris Protocol 265 through searches of Google. From all available identified records, removal of 1313 duplicate references by the Information Specialist (CD) resulted in a total of 3292 records for screening.

Figure 1. Study flow diagram.

Figure 1. (Continued)

independent
studies included
in qualitative and
quantitative
synthesis
(meta-analysis)

Two out of three review authors (AC, SF, JG) screened all records and excluded 3203 records on the basis of the abstract or title alone. The full texts of the remaining 89 records (53 references and 36 ongoing trial records) were assessed for inclusion against detailed eligibility criteria. Of these, 36 records describing 28 independent trials were excluded; details are listed in the [Characteristics of excluded studies](#) table. We also identified 14 ongoing trial records describing 13 independent trials which met the eligibility criteria for this review, but are yet to be completed or published (see [Characteristics of ongoing studies](#)). Two studies identified in the final search update appeared to meet eligibility criteria but were not fully evaluated; these studies were included as [Studies awaiting classification](#) and will be incorporated into future updates of this review. The remaining 37 records (28 references and nine ongoing trial records) described a total of 12 trials which are included in this review (one press release article described two trials ([Osiris Protocol 265](#); [Osiris Protocol 280](#))). All included studies were published in English.

Included studies

See [Characteristics of included studies](#) for full details of each study.

Trial design and setting

We identified a total of 12 eligible RCTs which included a total of 879 (range 14 to 260) randomised participants (two trials only reported the number of analysed participants which are included here ([Mareika 2016](#); [Osiris Protocol 265](#))). Two studies were phase three trials ([Osiris Protocol 265](#); [Osiris Protocol 280](#)), five were phase two trials ([Gao 2016](#); [Jurado 2017](#); [Kuzmina 2012](#); [Liu 2011](#); [Osiris Protocol 260](#)), one trial was a pilot study ([Ning 2008](#)), and in four trials the trial design phase was not reported. Ten trials compared MSCs with a control or placebo ([Gao 2016](#); [Ghavamzadeh 2010](#); [Kuzmina 2012](#); [Liu 2011](#); [Mareika 2016](#); [Ning 2008](#); [Osiris Protocol 265](#); [Osiris Protocol 280](#); [Wu 2013](#); [Zheng 2015](#)) and two trials ([Jurado 2017](#); [Osiris Protocol 260](#)) were mesenchymal stromal cell (MSC) dose-comparison trials with no control group. All were parallel two-arm trials. Four trials were published in abstract form only ([Ghavamzadeh 2010](#); [Mareika 2016](#); [Osiris Protocol 280](#); [Zheng 2015](#)) although in one trial, a submission to the Therapeutic Goods Administration, Australian Government to register Remestemcel-L (Prochymal) (subsequently withdrawn) was identified and data were extracted from documents relating to this application ([Osiris Protocol 280](#)). One further trial identified through searches of ongoing trial databases was unpublished; however a press release was identified and data were extracted from the information contained therein ([Osiris Protocol 265](#)). All other trials were published as full papers.

In seven trials, MSCs were administered as a prophylactic intervention for graft-versus-host disease (GvHD) ([Gao 2016](#);

[Ghavamzadeh 2010](#); [Kuzmina 2012](#); [Liu 2011](#); [Mareika 2016](#); [Ning 2008](#); [Wu 2013](#)), and in five trials MSCs were administered as treatment for GvHD ([Jurado 2017](#); [Osiris Protocol 260](#); [Osiris Protocol 265](#); [Osiris Protocol 280](#); [Zheng 2015](#)).

Five trials were performed in China ([Gao 2016](#); [Liu 2011](#); [Ning 2008](#); [Wu 2013](#); [Zheng 2015](#)) including one multicentre trial ([Gao 2016](#)). Three additional multicentre trials were performed in the USA ([Osiris Protocol 260](#)), USA/Australia/Canada ([Osiris Protocol 265](#)) and USA/Australia/Canada/Europe ([Osiris Protocol 280](#)). The remaining trials were performed in Spain ([Jurado 2017](#)), Iran ([Ghavamzadeh 2010](#)), Russia ([Kuzmina 2012](#)), and Belarus ([Mareika 2016](#)).

The median duration of follow-up in seven trials that administered MSCs prophylactically ranged from 10 months to 60 months, with individual participant follow-up ranging from one month ([Ghavamzadeh 2010](#)) to 70 months ([Gao 2016](#)). In three trials which administered MSCs as treatment for acute GvHD (aGvHD), participants were followed up for 90 days ([Osiris Protocol 260](#); [Osiris Protocol 265](#)) or 100 days ([Osiris Protocol 280](#)). In two trials of MSCs as treatment for chronic GvHD (cGvHD), the mean duration of follow-up was 13.4 months (MSC group) and 23.6 months (control group) ([Zheng 2015](#)), or 56 weeks ([Jurado 2017](#)).

Study participants

See [Table 1](#) for a summary of study participants. In 11 trials, participants had a range of haematological malignancies including acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic lymphoid leukaemia, chronic myeloid leukaemia, myelodysplastic syndrome and non-Hodgkins lymphoma. Of five trials which administered MSCs as therapy for GvHD, three included participants with aGvHD, either newly diagnosed ([Osiris Protocol 265](#)), requiring systemic steroid therapy ([Osiris Protocol 260](#)), or refractory to steroid therapy ([Osiris Protocol 280](#)), and in two trials participants had extensive cGvHD ([Jurado 2017](#); [Zheng 2015](#)). The extent of disease differed across trials with severe disease (defined as Grade III/IV or C/D) occurring in over 70% of patients in one trial ([Osiris Protocol 280](#)) compared with around 30% in another trial ([Osiris Protocol 260](#)). A third trial recruited patients with "newly diagnosed" GVHD with primarily involvement of the skin ([Osiris Protocol 265](#)). Multiple organ involvement was described in one trial ([Osiris Protocol 280](#)). One trial described a cohort of participants with class III thalassaemia major ([Ghavamzadeh 2010](#)).

The percentage of analysed participants who received the intervention ranged from 40% to 75% (median 50%). In the comparison of MSCs versus placebo, 364 participants (MSC group) and 268 participants (control group) were included in the analyses. One trial did not report the number of analysed participants in each intervention group ([Osiris Protocol 265](#)). In two trials which

compared two different doses of MSCs, analyses included 31 participants (15 received 8×10^6 cells/kg; 16 received 2×10^6 cells/kg) (Osiris Protocol 260), and 15 participants (six received 3×10^6 cells/kg; nine received 1×10^6 cells/kg) (Jurado 2017).

Five trials included only adults (Jurado 2017; Kuzmina 2012; Ning 2008; Osiris Protocol 260; Osiris Protocol 265), whereas six trials include both adults and children (Gao 2016; Ghavamzadeh 2010; Liu 2011; Mareika 2016; Osiris Protocol 280; Zheng 2015), although one trial focused on children and young adults (age range five to 24 years) (Mareika 2016). One trial was exclusively performed in children (age range 3.2 to 13.1 years) (Wu 2013). In eight trials which reported the distribution of males and females, the percentage of females in each study ranged from 20% to 59% (median 35.8%).

Haematopoietic stem cell transplant (HSCT) characteristics

Seven trials reported the origin of haematopoietic stem cells. One trial administered cells obtained from cord blood (Wu 2013), one trial administered cells taken from peripheral blood in all but one participant (Osiris Protocol 260); the remaining five trials obtained haematopoietic stem cells from a range of sources including bone marrow (mobilised with granulocyte colony-stimulating factor (G-CSF)) and peripheral blood. One trial included some patients who received a donor lymphocyte infusion (Osiris Protocol 265).

Human leukocyte antigen (HLA) matching of donors was reported in eight trials. Two trials reported donors as "matched related" or "matched sibling" (Ghavamzadeh 2010; Kuzmina 2012); two further trials used a combination of matched related and matched unrelated donors (Jurado 2017; Osiris Protocol 260), and one trial reported that donors were "HLA identical" (Ning 2008). Three trials reported the extent of matched or mismatched loci, (Gao 2016; Liu 2011; Wu 2013) (see [Characteristics of included studies](#) for further details).

Nine trials reported on conditioning regimens, but four of these were only listed as myeloablative (MAC) or reduced intensity (RIC) (see [Table 1](#)). One trial reported the use of one conditioning regimen for all patients (Liu 2011), and one (Ning 2008) used a similar regimen (total body irradiation (TBI) 10–12 Gy + cyclophosphamide) for all patients except one who received busulphan rather than TBI. Two trials reported using different regimens according to the disease (Gao 2016; Wu 2013).

Two trials (Mareika 2016; Zheng 2015) did not report the regimen used for GvHD prophylaxis, and one listed "standard of care" (Osiris Protocol 280) (see [Table 1](#)). One trial listed "methylprednisolone or equivalent" (Osiris Protocol 265), and eight used cyclosporine A together with one or more other immunosuppressants.

Study Interventions

See [Table 2](#) for a summary of study interventions.

MSCs were obtained from umbilical cord (Gao 2016; Wu 2013), from allogeneic bone marrow (Kuzmina 2012; Liu 2011; Mareika 2016; Ning 2008; Osiris Protocol 260; Osiris Protocol 265; Osiris Protocol 280) or from adipose tissue (Jurado 2017). Two trials did not report the origin of MSCs (Ghavamzadeh 2010; Zheng 2015). Six trials reported the MSC expansion protocol: five trials cultured MSCs using fetal bovine serum (Jurado 2017; Ning 2008; Osiris Protocol 260; Osiris Protocol 265; Wu 2013), one used platelet lysate (Kuzmina 2012) and one used a nutrient mixture of F12, 42%

MCDB-201 medium and 58% Dulbecco's Modified Eagle's medium (DMEM).

Co-transplantation of haematopoietic stem cells and MSCs was reported in five trials. MSCs were administered four hours prior to stem cell transplantation (Ghavamzadeh 2010; Ning 2008; Wu 2013), within 24 hours of stem cell transplantation (Liu 2011), or at the time of graft activation (Kuzmina 2012). The timing of MSC administration was not reported in two trials (Jurado 2017; Mareika 2016). MSCs were given post-HSCT in five trials, at four, five, six and seven months after stem cell transplantation (Gao 2016) and as treatment for GvHD in four trials (Osiris Protocol 260; Osiris Protocol 265; Osiris Protocol 280; Zheng 2015).

MSCs were administered at a median dose of approximately 10^5 cells/kg (Liu 2011; Ning 2008), 10^6 cells/kg (Ghavamzadeh 2010; Kuzmina 2012; Mareika 2016; Osiris Protocol 260; Osiris Protocol 265; Osiris Protocol 280; Wu 2013), or 10^7 cells/kg (Gao 2016; Zheng 2015), as a single infusion (Ghavamzadeh 2010; Kuzmina 2012; Liu 2011; Mareika 2016; Ning 2008; Wu 2013) or as multiple infusions, given as two infusions three days apart (Osiris Protocol 260), weekly infusions over four weeks (Zheng 2015), six infusions over four weeks (Osiris Protocol 265), eight infusions over four weeks (Osiris Protocol 280), or monthly over four months (Gao 2016).

Three trials administered a placebo infusion at the equivalent dose and schedule to the MSC trial arm, whereas in seven trials, no placebo was administered. One dose-comparison trial compared a high dose of MSCs (8×10^6 cells/kg) with a low dose of MSCs (2×10^6 cells/kg) (Osiris Protocol 260); the other compared a 3×10^6 cells/kg with a lower dose of 1×10^6 cells/kg (Jurado 2017).

Study outcomes

Clearly defined primary outcomes were reported in seven trials. In three trials of MSCs given as prophylaxis for GvHD, the primary outcome was defined as incidence of GvHD (Kuzmina 2012), or incidence and severity of aGvHD (Liu 2011) or cGvHD (Gao 2016). Additional primary outcomes in one trial were defined as time to engraftment and safety/tolerability of MSC co-infusion (Liu 2011). In four trials in which MSCs were administered as treatment for aGvHD, the primary outcome in three trials was defined as overall response (including complete and partial response) by day 28 (Osiris Protocol 260), or complete response of at least 28 days duration (Osiris Protocol 265; Osiris Protocol 280); the primary outcome in the fourth trial was safety (Jurado 2017).

Secondary outcomes were defined in seven studies (Gao 2016; Jurado 2017; Kuzmina 2012; Liu 2011; Osiris Protocol 260; Osiris Protocol 265; Osiris Protocol 280) and included safety of MSC infusion, overall survival, event-free or disease-free survival, disease relapse, incidence of acute or chronic GvHD, infection rates, time to engraftment, complete/partial/overall response of GvHD and time to response.

Five studies failed to define primary or secondary outcomes (Ghavamzadeh 2010; Mareika 2016; Ning 2008; Wu 2013; Zheng 2015). Study-specific reported outcomes are listed in the [Characteristics of included studies](#) tables.

Study funding

Nine trials reported the source of funding. Three trials were commercially sponsored by Osiris Therapeutics, Inc. (Osiris

Protocol 260; Osiris Protocol 265; Osiris Protocol 280), and six trials were supported by national government or academic research funding (Gao 2016; Jurado 2017; Kuzmina 2012; Liu 2011; Ning 2008; Wu 2013). No details of study funding were reported in the remaining three trials (Ghavamzadeh 2010; Mareika 2016; Zheng 2015).

Ongoing studies

We identified 13 ongoing trials (ACTRN12608000129381; ChiCTR-IIR-16007806; ChiCTR-INR-16008399; EUCTR2008-005594-35-BE; EUCTR2009-014980-38-BE; EUCTR2011-003237-33-NL; EUCTR2012-004915-30-NL; NCT00972660; NCT01045382; NCT01589549; NCT02241018; NCT02291770; NCT02770430) (see [Characteristics of ongoing studies](#) for full details).

Six trials administer MSCs as GvHD prophylaxis (ACTRN12608000129381; ChiCTR-IIR-16007806; ChiCTR-INR-16008399; EUCTR2008-005594-35-BE; EUCTR2009-014980-38-BE; NCT01045382) and seven trials give MSCs as treatment for either acute or chronic GvHD (EUCTR2011-003237-33-NL; EUCTR2012-004915-30-NL; NCT00972660; NCT01589549; NCT02241018; NCT02291770; NCT02770430).

Two trials have a planned follow-up of 10 years and are due to be completed in 2023 (EUCTR2011-003237-33-NL; EUCTR2012-004915-30-NL). Five other trials with planned follow-up ranging from 100 days to two years are due to be completed in December 2017 (NCT00972660), December 2018 (NCT02241018; NCT02770430), December 2019 (NCT02291770) and July 2023 (NCT01045382). One trial was due to have been completed in December 2016 (NCT01589549) but no publications relating to this trial have been identified. Five trials have not reported an expected completion date (ACTRN12608000129381; ChiCTR-IIR-16007806; ChiCTR-INR-16008399; EUCTR2008-005594-35-BE; EUCTR2009-014980-38-BE). The trialists in the latter two trials

have confirmed that these two trials are still ongoing. We have been unable to clarify the progress of the other three trials.

The planned enrolment for these 13 trials includes a total of 1532 participants. We will monitor their progress and when they are published, assuming eligibility, we will include them in future updates of the review.

Excluded studies

See [Characteristics of excluded studies](#) for further details.

Full-text screening excluded 28 trials (described in 36 records). Briefly, the reasons for exclusion were non-randomised treatment allocation (seven trials), single-arm trial with no control/placebo group (14 trials), intervention not relevant to this review (three trials), incorrect patient population (two trials), pre-clinical study (1 trial), and one study was withdrawn.

Studies awaiting classification

Two studies (Ghavamzadeh 2017; Xiang 2017) were identified during the final search update (December 2018) and have been included in [Studies awaiting classification](#), to be incorporated in future updates of this review. Both trials were of MSCs administered prophylactically and included a total of 134 participants (73 MSCs, 61 no MSCs). The first trial (Ghavamzadeh 2017) was reported as a conference abstract and included patients with beta-thalassaemia although it is unclear whether treatment allocation was randomised. The second trial (Xiang 2017) recruited children with acute lymphoblastic leukaemia.

Risk of bias in included studies

See the 'Risk of bias' tables within [Characteristics of included studies](#) for details of our assessment for each study and [Figure 2](#) for a summary.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Gao 2016	+	+	+	?	+	+	+
Ghavamzadeh 2010	?	?	?	?	+	-	?
Jurado 2017	?	?	-	-	?	?	+
Kuzmina 2012	?	?	-	-	+	?	+
Liu 2011	?	?	-	-	+	?	?
Mareika 2016	?	?	-	?	-	-	?
Ning 2008	?	?	-	?	+	-	+
Osiris Protocol 260	?	?	-	-	+	+	+
Osiris Protocol 265	?	?	+	+	-	-	-
Osiris Protocol 280	+	+	+	+	+	-	?
Wu 2013	?	?	-	?	+	?	+
Zheng 2015	?	?	-	?	+	-	?

Allocation

Two trials reported the method of random sequence generation and allocation and were considered to have a low risk of bias (Gao 2016; Osiris Protocol 280). In the first (Gao 2016), computer-generated random numbers were used and treatment allocation was retained in a data centre; in the second (Osiris Protocol 280), patients were randomised via a centralised interactive voice recognition system.

Three trials reported that they used stratified block randomisation (Kuzmina 2012; Ning 2008; Osiris Protocol 260) but the method of random sequence generation and allocation was not reported; the risk of selection bias was considered to be unclear in these trials. An unclear risk of selection bias was also attributed to the remaining seven trials which reported no details of random sequence generation or allocation (Ghavamzadeh 2010; Jurado 2017; Liu 2011; Mareika 2016; Osiris Protocol 265; Wu 2013; Zheng 2015).

Blinding

Trial participants were blinded to treatment through the use of a placebo in three trials (Gao 2016; Osiris Protocol 265; Osiris Protocol 280) which were considered to have a low risk of performance bias. A high risk of performance bias was attributed to eight trials, which were described either as open-label with no blinding attempted (Jurado 2017; Kuzmina 2012; Liu 2011; Osiris Protocol 260) or where no attempt at blinding or use of a placebo was described (Mareika 2016; Ning 2008; Wu 2013; Zheng 2015). One trial with an unclear risk of bias was described as "double-blind" but no details of a placebo were given (Ghavamzadeh 2010).

Two trials retained full blinding of all personnel until a specified post-analysis time point (Osiris Protocol 265; Osiris Protocol 280); these trials were considered to have a low risk of detection bias. A high risk of bias was attributed to four open-label trials in which no blinding of outcome assessors was reported (Jurado 2017; Kuzmina 2012; Liu 2011; Osiris Protocol 260). The remaining six trials did not report whether outcome assessors were blinded and in these trials the risk of detection bias was unclear (Gao 2016; Ghavamzadeh 2010; Mareika 2016; Ning 2008; Wu 2013; Zheng 2015).

Incomplete outcome data

The risk of attrition bias was generally low. In four trials, all randomised participants were included in the analysis (Ghavamzadeh 2010; Kuzmina 2012; Wu 2013; Zheng 2015); five further trials reported withdrawals but these were low in number and reasons for withdrawals or exclusions were given (Gao 2016; Liu 2011; Ning 2008; Osiris Protocol 260; Osiris Protocol 280); two trials performed intention-to-treat analyses (Gao 2016; Osiris Protocol 280). Two trials failed to report the number of randomised participants (Mareika 2016; Osiris Protocol 265); these trials were considered to have a high risk of attrition bias. One trial with an unclear risk of attrition bias originally included a randomised control group but this was dropped from the trial after a protocol amendment to a dose-comparison trial due to inadequate recruitment (Jurado 2017).

Selective reporting

Study protocols as defined by clinical trial records were identified for seven trials (Gao 2016; Jurado 2017; Kuzmina 2012; Osiris Protocol 260; Osiris Protocol 265; Osiris Protocol 280; Zheng 2015).

Of these, two trials reported all outcomes described in the protocol and were therefore considered to have a low risk of reporting bias (Gao 2016; Osiris Protocol 260).

Five trials had a high risk of reporting bias as they only reported limited results within a press release (Osiris Protocol 265) or conference abstract (Ghavamzadeh 2010; Mareika 2016; Osiris Protocol 280; Zheng 2015). In the Osiris Protocol 280 trial, results were extracted from licensing application documents published by the Australian Government Therapeutic Goods Administration; however not all outcome results were reported therein. A high risk of reporting bias was also attributed to one trial which was terminated early due to a higher median time to disease relapse in patients who received MSCs than in the control group (Ning 2008).

An unclear risk of reporting bias was attributed to two trials in which all outcomes in the protocol were reported, but the time points at which outcomes were measured differed to those described in the protocol (Jurado 2017; Kuzmina 2012). Finally, two trials reported all outcomes described in the methods; however no study protocol was identified to fully assess selective reporting and therefore the risk of reporting bias was unclear (Liu 2011; Wu 2013).

Other potential sources of bias

One trial was considered to be at a high risk of bias as no publications relating to this trial were identified other than a press release containing very few details (Osiris Protocol 265); there is no indication that this trial will be published in the future. One ongoing trial started in 2008 (ACTRN12608000129381) has not as yet been published and we have been unable to establish the current status of this trial. We therefore consider that there is a risk of publication bias.

An unclear risk of bias was attributed to five trials due to various factors. Two trials (Ghavamzadeh 2010; Liu 2011) included patients who received haematopoietic stem cells which originated from either bone marrow or peripheral blood but did not provide any information on the number of participants in each trial arm who received each graft type. Engraftment and GvHD rates can differ depending on the source of haematopoietic stem cells and there may be a risk of bias due to differences between trial arms. Two trials (Mareika 2016; Zheng 2015), which were published in abstract form only did not provide sufficient information to adequately assess additional sources of bias. Finally, for one trial data were extracted from licensing application documents published by the Australian Government Therapeutic Goods Administration which may contribute an additional source of bias (Osiris Protocol 280).

Effects of interventions

See: [Summary of findings for the main comparison MSCs compared to control/placebo for treating immune-mediated inflammation post-transplantation and in autoimmunity](#)

Results are presented separately below for the comparison of : mesenchymal stromal cells (MSCs) versus no MSCs, and for the comparison of different doses of MSCs. We identified 10 trials that compared the use of MSCs with no MSCs, and two trials that compared two different doses of MSCs. We did not identify any trials that compared different sources of MSCs.

For the primary outcomes of mortality and safety, and the secondary outcomes or adverse events, health-related quality of

life, relapse of malignant disease infection rates and engraftment, results are presented for prophylactic and therapeutic trials combined. Subgroup analyses are used to assess differences between prophylactic and therapeutic trials where relevant.

Use of MSCs versus no MSC treatment

Ten trials compared MSCs with a control or placebo group (Gao 2016; Ghavamzadeh 2010; Kuzmina 2012; Liu 2011; Mareika 2016; Ning 2008; Osiris Protocol 265; Osiris Protocol 280; Wu 2013; Zheng 2015) (see Table 1; Table 2) for a summary of participant characteristics and interventions). These 10 trials comprised a total of 833 randomised participants, including 372 randomised to MSCs and 269 randomised to the control group (one trial only reported the number analysed (included in these totals) (Mareika 2016) and in one trial the number randomised to each treatment arm was not reported (Osiris Protocol 265)). The main results for this comparison are shown in [Summary of findings for the main comparison](#).

Primary Outcomes

All-cause mortality

Nine trials measured mortality (Gao 2016; Kuzmina 2012; Liu 2011; Mareika 2016; Ning 2008; Osiris Protocol 265; Osiris Protocol 280; Wu 2013; Zheng 2015), although one trial did not report results for this outcome (Osiris Protocol 265) and in one trial, mortality was reported as percentage overall survival but it was unclear as to what these values represented (Mareika 2016). Of the remaining seven trials, five gave MSCs as prophylaxis (Gao 2016; Kuzmina 2012; Liu 2011; Ning 2008; Wu 2013) and two gave MSCs as treatment for GvHD (Osiris Protocol 280; Zheng 2015). Log hazard ratios with standard errors were estimated either using the methods of (Parmar 1998; Tierney 2007), method 7 (Gao 2016; Kuzmina 2012; Liu 2011) or method 9 (Osiris Protocol 280), or from individual patient data presented in the trial publications (Ning 2008; Wu 2013). One trial provided insufficient data to estimate log hazard ratios (Zheng 2015).

Analysis of mortality was considered to be inappropriate for treatment and prophylaxis trials pooled. Subgroup analysis showed insufficient evidence to detect a difference in the risk of mortality in either prophylactic trials (HR 0.85, 95% CI 0.50 to 1.42; participants = 301; studies = 5; I^2 = 34%; low-quality evidence) or therapeutic trials HR 1.12, 95% CI 0.80 to 1.56; participants = 244; studies = 1; very low-quality evidence) (test for subgroup differences: P = 0.38) (Analysis 1.1). No obvious outliers explained the moderate heterogeneity observed for this outcome in the five prophylactic trials.

Seven studies reported reasons for mortality (Gao 2016; Kuzmina 2012; Liu 2011; Ning 2008; Osiris Protocol 280; Wu 2013; Zheng 2015). In six trials in which MSCs were administered as prophylaxis for GvHD (Gao 2016; Kuzmina 2012; Liu 2011; Ning 2008; Wu 2013; Zheng 2015), relapse was the most common reason for death, accounting for 71.7% of deaths occurring in the MSC group compared with 58.6% in the control group. In the GvHD treatment trial (Osiris Protocol 280), the most frequent reason for death was infections/infestations, followed by immune system disorders and GvHD.

Safety of MSC infusion – acute toxicity, ectopic tissue formation or oncogenesis

Seven trials encompassing a total of 593 participants (334 MSCs, 259 no MSCs) reported measures of safety of MSC infusion (Gao 2016; Ghavamzadeh 2010; Kuzmina 2012; Liu 2011; Ning 2008; Osiris Protocol 280; Wu 2013). Results were presented descriptively in all seven trials. MSCs were well-tolerated in all trials, with no incidences of acute toxicity, ectopic tissue formation or oncogenesis reported in any study.

Secondary Outcomes

Health-related quality of life using validated scale

No trial reported health-related quality of life measures. One therapeutic trial (Osiris Protocol 280) described quote: "change from baseline in quality of life and Karnofsky/Lansky Performance Status assessments" as an additional efficacy variable of interest, but no results were reported for this outcome. One trial included quality of life in their protocol but no results for this outcome were reported (Zheng 2015).

Relapse of malignant disease

Two therapeutic trials reported relapse of malignant disease at short-term follow-up ($\leq$ 12 months) (Osiris Protocol 260; Osiris Protocol 280) (measured at 90 days and 180 days, respectively). There was insufficient evidence to detect a difference in the risk of relapse of malignant disease at short-term follow-up in the comparison of MSCs and no MSCs (RR 0.83, 95% CI 0.37 to 1.84; participants = 275; studies = 2; I^2 = 0%) (Analysis 1.2).

Six prophylaxis trials reported relapse of malignant disease at long-term follow-up ($>$ 12 months) (Gao 2016; Kuzmina 2012; Liu 2011; Mareika 2016; Ning 2008; Wu 2013). There was insufficient evidence to detect a difference in the risk of relapse of malignant disease at long-term follow-up in the comparison of MSCs and no MSCs (RR 1.08, 95% CI 0.73 to 1.59; participants = 323; studies = 6; I^2 = 0%; low-quality evidence) (Analysis 1.2).

Infection rates

Six studies reported infection as an outcome (Kuzmina 2012; Liu 2011; Mareika 2016; Ning 2008; Osiris Protocol 280; Wu 2013). Two studies reported results descriptively and stated that they observed either no differences in infectious complications (Kuzmina 2012), or a similar cumulative incidence of infections in both groups (Mareika 2016). Four studies (Liu 2011; Ning 2008; Osiris Protocol 280; Wu 2013) reported incidences of cytomegalovirus (CMV) infection, although in one study it was unclear whether any incidence of CMV infection was observed in the control group (Osiris Protocol 280). There was insufficient evidence to detect a difference in the risk of CMV infection in the comparison of MSCs and no MSCs (RR 1.03, 95% CI 0.71 to 1.50; participants = 100; studies = 3; I^2 = 0%) (Analysis 1.3). Three trials reported episodes of both bacterial and viral infections (Mareika 2016; Ning 2008; Osiris Protocol 280), although no trial reported significant differences between groups. Meta-analysis of these trials was not possible due to overlap in reporting of different infections across patients.

Engraftment

Engraftment was reported in five trials (Ghavamzadeh 2010; Liu 2011; Mareika 2016; Ning 2008; Wu 2013). The time to engraftment of platelets and neutrophils is summarised in Table 3. The times

were similar between the trial arms except for the cord blood HSCT study of Wu 2013, where both platelets and neutrophils engrafted at significantly faster rates with MSC treatment ($P = 0.004$ and $P = 0.003$, respectively). Two trials (Mareika 2016; Wu 2013) were observed to have high neutrophil engraftment times in the control group. In the case of Wu 2013, the HSCT source was cord blood which is known to lead to longer engraftment times. Therefore, this could potentially demonstrate a reduced engraftment time in patients who receive MSCs in this subgroup.

Figure 3. Forest plot of comparison: 1 MSCs vs. control/placebo, outcome: 1.4 Incidence of aGvHD (prophylactic trials).

Subgroup analysis according to type of disease (malignant versus non-malignant) revealed no differences between groups (test for subgroup differences: $P = 0.39$) (malignant disease: RR 0.83, 95% CI 0.60 to 1.14; participants = 199; studies = 5; non-malignant disease: RR 1.38, 95% CI 0.45 to 4.28; participants = 48; studies = 1) (Analysis 3.1).

Incidence of acute GvHD (prophylactic trials only)

Six trials reported the incidence of acute GvHD, classified as grades I to II (Ning 2008), grades I to III (Liu 2011), grades I to IV (Wu 2013), grades II to IV (Kuzmina 2012; Mareika 2016) and undefined in one trial (Ghavamzadeh 2010). There was insufficient evidence to detect a difference in the risk of acute GvHD in the comparison of MSCs and no MSCs (RR 0.86, 95% CI 0.63 to 1.17; participants = 247; studies = 6; $I^2 = 0\%$; low-quality evidence) (Analysis 1.4) (Figure 3).

Incidence of chronic GvHD (prophylactic trials only)

Six trials reported the incidence of chronic GvHD (Gao 2016; Kuzmina 2012; Liu 2011; Mareika 2016; Ning 2008; Wu 2013). Meta-analysis of these trials showed evidence that the risk of developing chronic GvHD was reduced in recipients of MSCs when compared to those who received no MSCs (RR 0.66, 95% CI 0.49 to 0.89; participants = 283; studies = 6; $I^2 = 0\%$; low-quality evidence) (Analysis 1.5) (Figure 4).

Figure 4. Forest plot of comparison: 1 MSCs vs. control/placebo, outcome: 1.5 Incidence of cGvHD (prophylactic trials).

Complete and partial response (therapeutic trials only)

Three trials measured complete and/or partial response of GvHD to treatment (Osiris Protocol 265; Osiris Protocol 280; Zheng 2015) although one trial did not report results for this outcome (Osiris Protocol 265).

In one trial which measured aGvHD response (Osiris Protocol 280), there was no evidence of a difference between treatment arms in

either complete response in the whole study cohort (RR 1.16, 95% CI 0.79 to 1.70; participants = 260, studies = 1; very low-quality evidence) (Analysis 1.6), or partial response reported in a paediatric subgroup (RR 2.00, 95% CI 0.20 to 19.6; participants = 28, studies = 1) (Analysis 1.7).

In one trial which measured cGvHD response (Zheng 2015), an "excellent response" was observed in 15/30 patients who received

MSCs compared with 1/10 patients in the comparator group, with no evidence of a difference between treatment arms (RR 5.00, 95% CI 0.75 to 33.21, participants = 40, studies = 1; very low-quality evidence) ([Analysis 1.8](#)). The equivalent number of participants who showed a partial response to treatment was 12/30 compared to 3/10 (RR 2.00, 95% CI 0.54 to 7.45, participants = 40, studies = 1) ([Analysis 1.9](#)).

Use of MSCs, dose A versus dose B

Two trials compared different doses of MSCs. One trial of 32 randomised participants compared 2×10^6 cells/kg with a higher dose of 8×10^6 cells/kg ([Osiris Protocol 260](#)), and one trial of 17 randomised patients compared 1×10^6 cells/kg with a higher dose of 3×10^6 cells/kg ([Jurado 2017](#)) (see [Table 1](#); [Table 2](#) for a summary of participant characteristics and interventions).

Primary Outcomes

All-cause mortality

In the [Osiris Protocol 260](#) trial, nine deaths occurred in 31 randomised participants; the number of deaths in each treatment arm was not reported. The cause of death was reported as progressive GvHD (4), disease relapse (1), central nervous system bleed (1), pneumonia (1), meningitis (1), and aspergillus enteritis (1). In the second trial ([Jurado 2017](#)), three deaths occurred in the low dose (1×10^6 cells/kg) group, all of which were due to progressive chronic GVHD. No deaths occurred in the control group.

Safety of MSC infusion – acute toxicity, ectopic tissue formation or oncogenesis

In both trials, all infusions were generally well-tolerated with no acute infusional toxicity and no ectopic tissue formation ([Jurado 2017](#); [Osiris Protocol 260](#)). Three participants were reported with adverse events related to intravenous drug infusion: one with pruritus on face, trunk and legs, one with high blood pressure and one with phlebitis and vein thrombosis of the upper left arm: all three recovered without sequelae ([Jurado 2017](#)).

Secondary Outcomes

Health-related quality of life using validated scale

This outcome was not reported.

Relapse of malignant disease

In one trial ([Osiris Protocol 260](#)), one disease relapse resulting in death occurred during the first 90 days in the high-dose MSC group. Two further relapses occurred over long-term follow-up but the treatment dose received by these two participants was not reported. No cases of disease relapse were reported in the second trial ([Jurado 2017](#)).

Infection rates

In the [Osiris Protocol 260](#) trial, infections were reported but the number of infections was not given separately for each treatment arm. Overall, 12 grade three infections (one adenovirus, four bacteraemia, five CMV viraemia and two BK virus-associated cystitis) and three grade four infections (pseudomonal pneumonia, enterococcal meningitis and aspergillus enteritis) were reported. Infections were also reported in the [Jurado 2017](#) trial in all but two patients in the low cell dose treatment arm, including viral infections (influenza A, CMV, parvovirus, herpes simplex,

herpes zoster, Epstein-Barr, rotavirus) and bacterial infections (cutaneous infection, *Clostridium difficile* diarrhoea, *Campylobacter jejuni* diarrhoea).

Engraftment

This outcome was not reported.

Incidence of acute GvHD (prophylactic trials only)

No prophylactic trials were identified for this comparison.

Incidence of chronic GvHD (prophylactic trials only)

No prophylactic trials were identified for this comparison.

Complete and partial response (therapeutic trials only)

In one trial there was no evidence of a difference between dosage groups in the proportion of participants with complete response (RR 0.76, 95% CI 0.51 to 1.14; participants = 31; studies = 1) ([Analysis 2.2](#)) or partial response of acute GvHD (grades II to IV) to treatment (RR 11.69, 95% CI 0.70 to 194.79; participants = 31; studies = 1) ([Analysis 2.3](#)) ([Osiris Protocol 260](#)). There was also no evidence of a difference between dosage groups in the proportion of patients with a complete response to chronic GVHD (RR 0.93, 95% CI 0.37 to 2.33; participants = 14; studies = 1) ([Analysis 2.4](#)) ([Jurado 2017](#)).

DISCUSSION

The main objective of this review was to examine the evidence for the safety and efficacy of mesenchymal stromal cells (MSC) for treating immune-mediated inflammation post-transplantation of haematopoietic stem cells.

Summary of main results

The available evidence from these trials showed that:

- Prophylactic administration of MSCs in conjunction with HSCT may reduce the risk of developing chronic graft-versus-host disease (cGvHD) when compared to no MSCs (RR 0.66, 95% CI 0.49 to 0.89; participants = 283; studies = 6; $I^2 = 0\%$; low-quality evidence).
- MSCs may make little or no difference to the risk of mortality (prophylactic trials: HR 0.85, 95% CI 0.50 to 1.42; participants = 301; studies = 5; low-quality evidence; therapeutic trials: HR 1.12, 95% CI 0.80 to 1.56; participants = 244; studies = 1; very low-quality evidence), or disease relapse (prophylactic trials: RR 1.08, 95% CI 0.73 to 1.59; participants = 323; studies = 6; low-quality evidence) compared to no MSCs.
- MSCs may make little or no difference to the risk of acute GvHD compared to no MSCs when administered prophylactically (RR 0.86, 95% CI 0.63 to 1.17; participants = 247; studies = 6; $I^2 = 0\%$; low-quality evidence).
- We are very uncertain whether administration of MSCs improves complete response (CR) (RR 1.16, 95% CI 0.79 to 1.70; participants = 260, studies = 1; very low-quality evidence) or partial response (RR 2.00, 95% CI 0.20 to 19.6; participants = 28, studies = 1) of acute GvHD compared to no MSCs when administered prophylactically.
- We are very uncertain whether administration of MSCs improves complete response (RR 5.00, 95% CI 0.75 to 33.21, participants = 40, studies = 1; very low-quality evidence) or partial response (RR 2.00, 95% CI 0.54 to 7.45, participants = 40, studies = 1)

of chronic GvHD compared to no MSCs when administered prophylactically.

- We are very uncertain whether a higher dose of MSCs reduces the risk of malignant disease relapse or complete (RR 0.76, 95% CI 0.51 to 1.14; participants = 31; studies = 1) or partial response (RR 11.69, 95% CI 0.70 to 194.79; participants = 31; studies = 1) to acute GvHD.

Overall completeness and applicability of evidence

This review provides the most up-to-date evidence for the role of MSCs as treatment or prophylaxis for GvHD in individuals who have received a haematopoietic stem cell transplant (HSCT) for a haematological condition. We identified 12 randomised trials which met the inclusion criteria for this review: 10 trials compared MSCs to no MSCs (control or placebo) involving a total of 833 randomised participants, and two trials of 47 randomised participants compared different doses of MSCs. One trial was in patients with thalassaemia, the remaining 11 trials were in patients with haematological malignancies. Seven trials administered MSCs as a prophylactic intervention for GvHD, whereas five trials gave MSCs as treatment for GvHD. MSCs were derived from umbilical cord in two trials, bone marrow in seven trials and adipose tissue in one trial; two trials failed to report the origin of MSCs. In the comparison of MSCs with no MSCs, cells were administered at a dose of between 10^5 and 10^7 cells/kg in either a single dose (six trials) or in multiple doses (four trials). The dose-comparison trials compared 2×10^6 cells/kg with 8×10^6 cells/kg in two infusions, or 1×10^6 cells/kg with 3×10^6 cells/kg in a single infusion. The median duration of follow-up in seven trials which administered MSCs prophylactically ranged from 10 months to 60 months. In three trials of MSCs as treatment for acute GvHD, (aGvHD), participants were followed up for 90 or 100 days. In two trials of MSCs as treatment for cGvHD, the mean duration of follow-up was 13.4 months (MSC group) and 23.6 months (control group), or 56 weeks.

There is a high degree of clinical heterogeneity arising from differences in both participant characteristics and interventions across trials. In particular, differences in the underlying HSCT (source and extent of human leukocyte antigen (HLA) matching) as well as the timing, dosage, source and production protocols of the MSCs administered may all contribute to the expected clinical heterogeneity across these studies. Notably, for many outcomes values of I^2 were 0%. However, I^2 values are known to be underestimated, especially when there are few events or a limited number of studies included in a meta-analysis (Huedo-Medina 2006; Ioannidis 2007).

We only identified two trials comparing different doses of MSCs and we found no trials which compared MSCs from different sources (e.g. bone marrow versus cord). The applicability of evidence is therefore limited when considering the question of whether MSCs of a particular source or dose are efficacious in a specific patient population. Across all outcomes, there is insufficient data to show clearly whether MSCs have a beneficial (or detrimental) effect.

One trial (Osiris Protocol 280) suggested that MSCs showed a beneficial effect in a paediatric subgroup and in patients with steroid-refractory aGvHD occurring in the liver and gut. However, we deemed this trial to have a high risk of reporting bias as it was only reported as a conference abstract and press release. We did not identify a sufficient number of trials to perform our proposed

subgroup analysis by participant age (adults versus paediatric) or specific organ involvement.

No trial reported quality of life as an outcome.

Quality of the evidence

We have summarised the quality of evidence for the main comparison of MSCs versus no MSCs in the [Summary of findings for the main comparison](#). Our GRADE assessment found that the overall quality of evidence was low or very low for all included outcomes; all outcomes were downgraded due to risk of bias and imprecision due to the low number of participants included in the analyses. Only two trials reported clearly their methods of random sequence generation and allocation concealment. Only three trials were adequately blinded with the use of a placebo arm. Finally, a high risk of reporting bias was attributed to six trials: four were published in conference abstract form only (Ghavamzadeh 2010; Mareika 2016; Osiris Protocol 280; Zheng 2015) (although one (Osiris Protocol 280) was the subject of a detailed licensing application to the Therapeutic Goods Administration of the Australian Government, see (Acknowledgements)), one was reported as press release only with few details (Osiris Protocol 265), and one trial was terminated early prematurely due to an apparent increased risk of disease relapse in patients who received MSCs (Ning 2008). The majority of trials included fewer than 100 randomised participants in total and only one trial included over 200 participants, leading to imprecision.

Three trials were undertaken by Osiris Therapeutics, Inc. (Osiris Protocol 260; Osiris Protocol 265; Osiris Protocol 280), including the two largest trials included in this review which compared MSCs to no MSCs and the reporting of two of these trials was extremely limited, with a high risk of reporting bias.

Publication bias was also considered a possibility due to one ongoing trial which was started in 2008 but has not resulted in any associated publications.

There was notable clinical heterogeneity in the stem cell sources used for transplantation, types and stages of malignant disease being treated, definitions of outcomes, as well as differences in study quality. We were unable to perform sensitivity analyses due to the paucity of suitable studies, but these will be addressed in future updates of this review as further randomised controlled studies are published.

Potential biases in the review process

We are not aware of any obvious biases with the review process. We conducted an extensive search, which included ongoing trial databases. We also contacted researchers in the field to identify any further as yet unpublished trials. No restrictions were placed on the language in which the paper was originally published or its publication status. We performed all screening and data extraction in duplicate by two review authors and resolved any discrepancies through discussion. We were unable to perform a formal assessment of publication bias due to the low number of included studies.

The outcomes defined in this review were revised from the original protocol in accordance with the change of scope of the review to include trials which administered MSCs as prophylaxis for GvHD

as well as those in which MSCs were given therapeutically (see [Differences between protocol and review](#)). These revised outcomes were defined *a priori* in accordance with our expectations for studies of this nature, and were not biased by the outcomes reported in individual studies.

None of the review authors were involved in the included or excluded studies.

Agreements and disagreements with other studies or reviews

A systematic review has been published on the safety of MSCs for clinical use ([Lalu 2012](#)) and our review is consistent with their finding that MSCs are safe for use in patients. Systematic reviews have been published on the use of MSC for prevention and treatment of GvHD ([Chen 2015](#); [Hashmi 2016](#); [Kallekleiv 2016](#)). These included non-randomised trials, which were excluded from this review, and the authors restricted their analysis to treatment of aGvHD ([Chen 2015](#); [Hashmi 2016](#)) or to co-transplantation of MSC and HSC ([Kallekleiv 2016](#)). These reviews conclude that, while MSCs appear to be safe and there are some indications of efficacy, there is a need for more prospective, randomised controlled trials (RCTs) to establish whether MSCs convey a significant benefit in the prevention or treatment of aGvHD. Kallekleiv and colleagues found a trend ($P = 0.015$) towards reduced rates of cGvHD with the prophylactic use of MSCs from analysis of three RCTs also included in our review ([Liu 2011](#); [Ning 2008](#); [Wu 2013](#)). In our review we included an additional three RCTs ([Gao 2016](#); [Kuzmina 2012](#); [Mareika 2016](#)) and also found that MSCs may reduce the risk of chronic GvHD (RR 0.66, 95% CI 0.49 to 0.89; participants = 283; studies = 6; $I^2 = 0\%$; low-quality evidence). A recent systematic review of MSCs for cGvHD prophylaxis ([Wang 2018](#)) included six trials and concluded that MSCs significantly reduced the incidence of cGvHD, with risk estimates similar to those found in this Cochrane Review (RR 0.63, 95% CI 0.46 to 0.86). Wang and colleagues also performed separate analyses for adults and children, and found that this effect was only seen in children, although it should be noted that only two studies were included in each group and there was no significant difference between adults and children, as indicated by the overlapping confidence intervals. We will continue to monitor the available randomised trials and update this review accordingly.

AUTHORS' CONCLUSIONS

Implications for practice

The main positive finding from this review is the support for prophylactic use of mesenchymal stromal cells (MSCs) to reduce rates of chronic graft-versus-host disease (cGvHD) although the quality of evidence is currently low. This debilitating complication of allogeneic transplantation has been increasing in frequency, associated with the increasing age of the patient population and preference for mobilised peripheral blood rather than bone marrow as a stem cell source ([Flowers 2015](#)). Treatment options are limited for steroid refractory cGvHD, and MSCs may represent a safe preventative therapy although further confirmatory trials are required before this can be implemented into clinical practice. We have found no conclusive evidence for the use of MSCs in reducing all-cause mortality in people with acute or chronic GvHD.

Implications for research

Replication of the findings for cGvHD with further well-powered randomised controlled trials (RCTs) is needed to provide robust support for recommending the use of MSC as a complement or alternative to current standards of prophylaxis. The reviewed studies differed in the timing, dosage, source and production protocols of MSC administered, and these are all parameters that will need to be assessed in order to determine effective treatment regimens. Whether MSCs are more efficacious in paediatric patients and for different organ involvements are other areas for future investigation. Given the lack of conclusive evidence to date, future trials must be directed at achieving sufficient power to support or not the use of MSCs for treatment and prevention of GvHD and the factors discussed above which may affect efficacy. Furthermore, trials should be prospectively registered with a full study protocol with comprehensive details of the study design, participants and interventions, and results should be reported in full.

MSCs are an area of intense research activity, and an increasing number of trials have been undertaken or are planned. Despite a number of reports of positive outcomes from the use of MSCs for treating acute GvHD (aGvHD), the evidence to date from RCTs has not supported the conclusion that they are an effective therapy. Therefore, it is imperative that future trials are directed at determining the potential of MSCs to treat aGvHD. There is low-quality evidence that prophylactic use of MSCs may reduce the risk of cGvHD. Nevertheless, given the current lack of effective treatment strategies for preventing or treating cGvHD, this finding is encouraging and prompts renewed efforts by researchers to demonstrate significant efficacy. New trial evidence will be incorporated into future updates of this review, which may better establish any role for MSCs in clinical applications for GvHD (e.g. treatment or prophylaxis, acute or chronic, paediatric or adult, organ involvement).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Gao 2016

Methods	<p>Type of study: a phase 2, multicentre, placebo-controlled, randomised trial</p> <p>Countries where study performed: China (multicentre)</p> <p>Dates of recruitment: May 2009 - March 2013</p> <p>Duration of follow-up: median 51 months (range 24-70 months)</p> <p>Study funding: supported by the Stem Cell Pilot Project of Chinese Academy of Sciences, Chinese National Natural Science Foundation, Chinese Overseas Scholars Cooperative Research Foundation, Arm Key Foundation, Chinese Degree and Graduate Education Research project and by research funds from Clinical Foundation of Xinqiao Hospital</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> HLA-haplo HSCT who patients did not have GvHD Patient is < 60 years of age on the day of signing the informed consent Patient KPS score > 60 No serious organ dysfunction Expected survival > 3 months Patient has voluntarily agreed to participate by giving written informed consent Patient is available for periodic blood sampling, study related assessments, and management at the treating institution for the duration of the study <p>Exclusion criteria</p> <ul style="list-style-type: none"> Patient has serious organ dysfunction Patient has leukaemia combined with other cancer Patient presented clinical signs of brain dysfunction or severe mental illness who can not comply with the study protocol Patient was unable to schedule follow-up Patient was unable to guarantee the completion of the treatment plan and the necessary follow-up observation Patient has active systemic infection or GvHD requiring treatment Patient has known hypersensitivity to any components of MSCs <p>Number of participants randomised: 124 (62 MSC, 62 placebo)</p> <p>Number of participants analysed: 124 (62 MSC, 62 placebo)</p> <p>Age</p> <p>Intervention group: < 18 years: 15 (24.2%); 18-40 years: 39 (62.9%); > 40 years : 8 (12.9%)</p> <p>Comparator group: < 18 years: 13 (21.0%); 18-40 years: 43 (69.4%); >40 years: 6 (9.7%)</p> <p>Gender</p> <p>Intervention group: 46.8% male</p>

Gao 2016 (Continued)

Comparator group: 48.4% male

Disease

Intervention group: AML 43 (69.4%); ALL 14 (22.6%); MDS 5 (8.1%)

Comparator group: AML 42 (67.7%); ALL 16 (25.8%); MDS 4 (6.5%)

Disease stage

Intervention group: CR1 48 (77.4%); CR2 8 (12.9%); PR 6 (9.7%)

Comparator group: CR1 39 (62.9%); CR2 15 (24.2%); PR 8 (12.9%)

GvHD involvement

No aGvHD, or controlled within 100 days (inclusion criteria)

Source of HSCT: n/r

HSCT donor matching

Intervention group: 1 mismatch 5 (8.1%); 2 mismatch 20 (32.3%); 3 mismatch 37 (59.7%)

Comparator group: 1 mismatch 3 (4.8%); 2 mismatch 30 (32.3%); 3 mismatch 39 (62.9%)

Conditioning regimen: all patients received a MAC regimen. Patients with ALL received TBI plus Ara-C, CY and ATG. Patients with AML and those with MDS received CCNU, Ara-C, BU, CY, and ATG

GvHD treatment: N/A

GvHD prophylaxis: CSA, MMF and short term MTX

Interventions	Intervention arm: UC-derived MSCs: 3x10 ⁷ cells/100mL/month at +4,+5,+6 and +7 months post-HSCT	
	Comparator arm: normal saline: 100mL/month at +4,+5,+6 and +7 months post-HSCT	
	Expansion protocol: n/r	
	Prophylactic or therapeutic: prophylactic	
Outcomes	Primary outcome <ul style="list-style-type: none">• Incidence and severity of cGvHD Secondary outcomes <ul style="list-style-type: none">• Safety of umbilical cord-derived MSC infusion• Overall survival• Event-free survival Exploratory endpoints <ul style="list-style-type: none">• Change of T/B/NK cell subsets• Change of Th1:Th2 cells	
Notes	Trial registration identifier: ChiCTR-IOR-15006330	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers were generated from a computer by a statistician.

Gao 2016 (Continued)

Allocation concealment (selection bias)	Low risk	Treatment allocation was retained in the data centre.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was described as "double-blind" and a placebo was used. Both treatment preparations (MSCs and saline placebo) were produced by the same institute to ensure identical volume, consistency, shape and colour.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as "double-blind" but blinding of outcome assessors was not specifically reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was performed by Intention-to-treat; loss to follow-up and discontinuation of treatment was documented in detail for each group.
Selective reporting (reporting bias)	Low risk	All outcomes defined in the protocol were reported.
Other bias	Low risk	No other sources of bias were detected.

Ghavamzadeh 2010

Methods	<p>Type of study: a "double-blind", randomised controlled trial</p> <p>Countries where study performed: Iran</p> <p>Dates of recruitment: November 2006 - October 2009</p> <p>Duration of follow-up: median 10 months (range 1 - 28 months)</p> <p>Study funding: n/r</p>
Participants	<p>Inclusion criteria: Class III thalassaemia major patients requiring HSCT</p> <p>Exclusion criteria: n/r</p> <p>Number of participants randomised: 48 (25 MSC, 23 no MSC)</p> <p>Number of participants analysed: 48 (25 MSC, 23 no MSC)</p> <p>Age</p> <p>Intervention group: median 17 years</p> <p>Comparator group: median 16 years</p> <p>Gender</p> <p>Intervention group: 68% male</p> <p>Comparator group: 52% male</p> <p>Disease</p> <p>Intervention group: thalassaemia major</p> <p>Comparator group: thalassaemia major</p> <p>Disease stage</p>

Ghavamzadeh 2010 (Continued)

Intervention group: class III

Comparator group: class III

GvHD involvement

N/A

Source of HSCT: PB or BM

HSCT donor matching

Intervention group: "HLA matched related donor"

Comparator group: "HLA matched related donor"

Conditioning regimen: CY or fludarabine-based regimen

GvHD treatment: N/A

GvHD prophylaxis: CSA and MTX

Interventions	Intervention arm: MSCs: $1.45-1.8 \times 10^6$ cells/kg given in single infusion intravenously 4 hours prior to HSCT Comparator arm: no MSCs Expansion protocol: n/r Prophylactic or therapeutic: prophylactic
Outcomes	Primary outcome: n/r Secondary outcomes: n/r Reported outcomes <ul style="list-style-type: none"> • Safety of infusion • Time to neutrophil engraftment • Time to platelet engraftment • Incidence of acute GvHD grade III-IV • Mortality
Notes	Trial registration identifier: N/A <p>We have not identified any further publications associated with this trial and have been unable to confirm with the study authors whether further publications are planned.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as "double-blind" but no further details were given.

Ghavamzadeh 2010 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as "double-blind" but no further details were given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The abstract reports that 48 patients were enrolled, and all were included in the reported results.
Selective reporting (reporting bias)	High risk	No protocol was described or identified and this study has only been reported as a conference abstract.
Other bias	Unclear risk	Patients received quote: "either bone marrow or peripheral blood stem cells". Engraftment and GvHD rates can differ between these two stem cell sources, information as to how many in each arm received which graft type was not provided.

Jurado 2017

Methods	<p>Type of study: a phase 1/2, open-label, dose-comparison randomised trial</p> <p>Countries where study performed: Spain</p> <p>Dates of recruitment: n/r</p> <p>Duration of follow-up: 60 weeks</p> <p>Study funding: supported by the Consejería de Salud (Junta de Andalucía)</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Chronic extensive GvHD never received therapy for cGvHD de novo or quiescent chronic extensive GvHD <p>Exclusion criteria</p> <ul style="list-style-type: none"> Concomitant severe systemic infection Oncologic or haematological condition relapse Estimated life expectancy < 1 week No informed consent <p>Number of participants randomised: 17 (6 MSC 3 x 10⁶ cells/kg; 9 MSC 1 x 10⁶ cells/kg; 2 no MSCs)</p> <p>Number of participants analysed: 14 (5 MSC 3 x 10⁶ cells/kg; 9 MSC 1 x 10⁶ cells/kg) [NB: control group not included in analysis, see notes below]</p> <p>Age</p> <p>Intervention group (3 x 10⁶ cells/kg): mean 45.5 years (SD 7.92) years</p> <p>Comparator group (1 x 10⁶ cells/kg): mean 51.1 years (SD 10.85) years</p> <p>Gender</p> <p>Intervention group: 33.3% male</p> <p>Comparator group: 80.0% male</p> <p>Disease</p>

Jurado 2017 (Continued)

Intervention group: lymphoma 3, acute leukaemia 2, myeloma 0

Comparator group: lymphoma 6, acute leukaemia 2, myeloma 1

Disease stage

n/r

GvHD involvement

Intervention group: cGvHD moderate 3, severe 2

Comparator group: cGvHD moderate 4, severe 5

Source of HSCT: PBSC
HSCT donor matching

Intervention group: matched related donor 7; matched unrelated donor 2

Comparator group: matched related donor 3; matched unrelated donor 2

Conditioning regimen: 3 MAC, 11 RIC
GvHD treatment: N/A
GvHD prophylaxis: CSA and prednisone

Interventions	Intervention arm: adipose tissue-derived MSCs: 3 x 10 ⁶ cells/kg given as a single infusion during the first week Comparator arm: adipose tissue-derived MSCs: 1 x 10 ⁶ cells/kg given as a single infusion during the first week Expansion protocol: FBS Prophylactic or therapeutic: therapeutic	
Outcomes	Primary outcome <ul style="list-style-type: none">• Safety (number of adverse events) Secondary outcomes <ul style="list-style-type: none">• Percentage of patients with reduction of corticosteroids at weeks 7, 20 and 42, started immunosuppressive treatment and percentage of patients at week 56 have been suspended on full immunosuppressive treatment• Overall survival and disease-free survival at 12 months• Changes in lymphocyte subsets and levels of inflammatory and anti-inflammatory cytokines in each group	
Notes	Trial registration identifier: NCT01222039 Two patients were randomised to a control group but excluded from the study after a protocol amendment to change the trial design to a dose-comparison study due to inadequate recruitment.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported.

Jurado 2017 (Continued)

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an open-label trial. No blinding of outcome assessors was reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two patients originally randomised to a control group were dropped from the trial after a protocol amendment to a dose-comparison trial due to inadequate recruitment.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in the trial registration record were reported, although the time points at which outcomes were measured differed in the published results.
Other bias	Low risk	No other sources of bias were detected.

Kuzmina 2012

Methods	<p>Type of study: a phase 2, open-label, randomised controlled trial</p> <p>Countries where study performed: Russia</p> <p>Dates of recruitment: October 2008 - April 2014</p> <p>Duration of follow-up: 60 months</p> <p>Study funding: Supported by grants from the Moscow Government and the Russian Foundation for Basic Research</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Aged 18-60 years • Allo-HSCT from related donors <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Severe infection • Relapse • Admission to ICU • Refusal of research • Patients with graft failure <p>Number of participants randomised: 77 (39 MSC; 38 no MSC)</p> <p>Number of participants analysed: 77 (39 MSC; 38 no MSC)</p> <p>Age</p> <p>In preliminary study of 37 participants:</p> <p>Intervention group: median 34 years (range 20-63 years)</p> <p>Comparator group: median 29 years (range 19-60 years)</p>

Kuzmina 2012 (Continued)

Gender

In preliminary study of 37 participants:

Intervention group: 42.2% male (in 19 participants)

Comparator group: 39.0% male (in 18 participants)

Disease

In preliminary study of 37 participants:

Intervention group: AML/MDS 14, ALL 2, CML 3, CLL 0

Comparator group: AML/MDS 10, ALL 4, CML 3, CLL 1

Disease stage

In preliminary study of 37 participants:

Intervention group: CR 19 (100.0%)

Comparator group: CR 15 (83.3%); PR 3 (16.7%)

GvHD involvement:

N/A

Source of HSCT: BM

HSCT donor matching:

Intervention group: "HLA matched siblings"

Comparator group: "HLA matched siblings"

Conditioning regimen: 43 MAC (CY, BU), 34 RIC (fludarabine, BU, ATG)

GvHD treatment: N/A

GvHD prophylaxis: CSA combined with MTX, some patients additionally received MMF or prednisolone.

Interventions

Intervention arm: BM-derived MSCs: $1.2 (0.9 \text{ to } 1.65) \times 10^6$ cells/kg

Comparator arm: No MSCs

Expansion protocol: PL

Prophylactic or therapeutic: prophylactic

Outcomes
Primary outcome

- GvHD incidence (every 30 days for 1 year after HSCT)

Secondary outcomes

- Overall survival
- Relapse survival
- Infection rate

Additional reported outcomes

- Relapse frequency
- Transplant rejection
- Adverse events

Kuzmina 2012 (Continued)

- Lymphocyte proliferation
- Gene expression levels

Notes

Trial registration identifier: NCT01941394

Preliminary results published in 2012 for 37 participants (19 MSC; 18 no MSC)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors state that quote: "block randomisation was performed" but no further details on the method of randomisation were reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label trial. Patients' own platelets were used for MSC expansion and it is unclear whether MSCs were expanded for the control group.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an open-label trial. No blinding of outcome assessors was reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in the trial registration record were reported, although the time points at which outcomes were measured differed in the published results.
Other bias	Low risk	No other sources of bias were detected.

Liu 2011

Methods

Type of study: a phase 2, open-label, randomised controlled trial

Countries where study performed: China

Dates of recruitment: June 2007 - June 2008

Duration of follow-up: MSC: median 23.5 months (range 3.8 - 32.5 months); no MSC: median 24.6 months (0.7 - 33.5 months)

Study funding: supported by the National High Technology Research and Development Program of China

Participants

Inclusion criteria

- Patients with malignant haematological disease in remission requiring HSCT but with no matched donor.
- In remission at time of transplantation
- No serious organ dysfunction or active infections

Exclusion criteria

Mesenchymal stromal cells as treatment or prophylaxis for acute or chronic graft-versus-host disease in haematopoietic stem cell transplant (HSCT) recipients with a haematological condition (Review)

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Liu 2011 (Continued)

- Active malignancy, serious organ dysfunction or active infection.
- Relapse
- Sibling-matched donor
- Obesity
- Insufficient MSCs

Number of participants randomised: 60 (30 MSC; 30 no MSC)

Number of participants analysed: 55 (27 MSC; 28 no MSC)

Age

Intervention group: median 30 years (range 14 - 46 years)

Comparator group: median 31.5 years (range 12 - 48 years)

Gender

Intervention group: 68% male

Comparator group: 74% male

Disease

Intervention group: ALL 8 (29.6%), AML 13 (48.1%), CML 6 (20.0%). High risk disease 6 (20.0%)

Comparator group: ALL 16 (57.1%), AML 7 (25.0%), CML 5 (17.9%). High risk disease 6 (21.4%)

Disease stage

Intervention group: CR1 23 (85.1%), CR2 4 (14.9%)

Comparator group: CR1 24 (85.7%), CR2 4 (14.3%)

GvHD involvement

N/A

Source of HSCT: G-CSF mobilised BM and PBSC

HSCT donor matching:

Intervention group: HLA-matched loci: 3 (17); 4 (6); 5 (4)

Comparator group: HLA-matched loci: 3 (16); 4 (10); 5 (2)

Conditioning regimen: BU, CA, Ara-C, CY, ATG

GvHD treatment: N/A

GvHD prophylaxis: CSA given from day -9 to 6 months post-transplantation at 1.25 mg/kg to prevent GvHD. The dose of CSA was adjusted after monitoring serum levels to maintain a concentration within the range of 150–250 ng/mL; the CSA treatment was tapered starting at day p90 and discontinued on day p180. MTX was given on day p1 at a dose of 15 mg/m², and the dose was decreased to 10 mg/m² on days p3, p6, and p11 post-transplantation

Interventions

Intervention arm: BM-derived MSCs: 3-5 x 10⁵ cells/kg administered pre-infusion within 24 hours

Comparator arm: no MSCs

Expansion protocol: nutrient mixture of F12, 42% MCDB-201 medium and 58% DMEM

Prophylactic or therapeutic: prophylactic

Outcomes

Primary outcomes

Liu 2011 (Continued)

- Safety and tolerability of MSC coinfusion
- Time to marrow engraftment
- Incidence and severity of acute GvHD

Secondary outcomes

- Relapse
- Overall survival
- Engraftment
- Incidence of cGvHD
- CMV viraemia
- Cytokine levels

Notes	Trial registration identifier: N/A	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label trial. No blinding of participants or personnel was reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an open-label trial. No blinding of outcome assessors was reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and exclusions were low and balanced between trial arms; reasons for withdrawals were provided.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported in the methods were reported, but no protocol was available to fully assess selective reporting
Other bias	Unclear risk	Patients received quote: "either bone marrow or peripheral blood stem cells". Engraftment and GvHD rates can differ between these two stem cell sources, information as to how many in each arm received which graft type was not provided.

Mareika 2016

Methods	Type of study: a randomised controlled trial Countries where study performed: Belarus Dates of recruitment: n/r Duration of follow-up: median 38 months (range 5.7 - 59.4 months)
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Mareika 2016 (Continued)

	Study funding: n/r
Participants	<p>Inclusion criteria: children/young adults with acute leukaemia</p> <p>Exclusion criteria: n/r</p> <p>Number of participants randomised: n/r</p> <p>Number of participants analysed: 22 (10 MSC; 12 no MSC)</p> <p>Age: median 13 years (groups "identical" with respect to age)</p> <p>Gender: n/r (groups "identical" with respect to gender)</p> <p>Disease</p> <p>Intervention group: AML 2 (20.0%); ALL 8 (80.0%)</p> <p>Comparator group: AML 4 (33.3%); ALL 7 (58.3%); MDS 1 (8.3%)</p> <p>Disease stage</p> <p>Intervention group: n/r</p> <p>Comparator group: n/r</p> <p>GvHD involvement:</p> <p>N/A</p> <p>Source of HSCT: n/r</p> <p>HSCT donor matching: n/r</p> <p>Conditioning regimen: n/r</p> <p>GvHD treatment: N/A</p> <p>GvHD prophylaxis: n/r</p>
Interventions	<p>Intervention arm: BM-derived MSCs: $1.56 \pm 0.4 \times 10^6$ cells/kg in single dose, "co-transplantation" with HSCT.</p> <p>Comparator arm: no MSCs</p> <p>Expansion protocol: n/r</p> <p>Prophylactic or therapeutic: prophylactic</p>
Outcomes	<p>Primary outcome: n/r</p> <p>Secondary outcomes: n/r</p> <p>Reported outcomes:</p> <ul style="list-style-type: none"> • Incidence of acute and chronic GvHD • Relapse • Episodes of infection in post-transplant period • Survival • Immunological parameters including NK and B cells • Leukocyte/neutrophil/platelet recovery
Notes	Trial registration identifier: N/A

Mareika 2016 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants or personnel was not reported; no placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	No withdrawals or exclusions were described but the number of randomised participants was not reported.
Selective reporting (reporting bias)	High risk	No protocol was described or identified and this study has only been reported as a conference abstract.
Other bias	Unclear risk	In this conference abstract there was insufficient information to assess any other potential sources of risk of bias.

Ning 2008

Methods	<p>Type of study: an open-label, randomised controlled trial</p> <p>Countries where study performed: China</p> <p>Dates of recruitment: March 2003 - March 2004</p> <p>Duration of follow-up: median 36.6 months (range 0.6 - 44.0 months)</p> <p>Study funding: funded by the National 863 Program, Ministry of Science and Technology, People's Republic of China</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • HLA-identical sibling donor • Eastern Cooperative Oncology Group performance status of 0 or 1 • Adequate visceral organ function (including a left ventricular ejection fraction of at least 50%) • Forced expiratory volume in 1 second and diffusion of carbon monoxide greater than 50% of predicted • Serum direct bilirubin less than 2.0 mg per 100 mL • Actual or calculated creatinine clearance greater than 60 mL min⁻¹ <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Major central nervous system dysfunctions • Active infection <p>Number of participants randomised: 30 (15 MSC; 15 No MSC)</p>

Ning 2008 (Continued)

Number of participants analysed: 25 (10 MSC; 15 No MSC)

Age

Intervention group: median 38 years (range 17 - 52 years)

Comparator group: median 37 years (range 16- 61 years)

Gender

Intervention group: 73.3% male

Comparator group: 86.7% male

Disease:

Intervention group: AML 8 (53.3%); ALL 2 (13.3%); CML 4 (26.7%); MDS 1 (6.7%)

Comparator group: AML 7 (46.7%); ALL 2 (13.3%); CML 4 (26.7%); MDS 1 (6.7%); NHL 1 (6.7%)

Disease stage

Intervention group: CR1 9 (60.0%); CP 3 (20.0%); first relapse 1 (6.7%); CP2 1 (6.7%); RAS 1 (6.7%)

Comparator group: CR1 8 (53.3%); CR2 1 (6.7%); CP 2 (13.3%); CP2 2 (13.3%), RAS 1 (6.7%), no relapse 1 (6.7%)

GvHD involvement

N/A

Source of HSCT

Intervention group: PBSC 7 (46.7%), BM 5 (33.3%), PBSC+BM 3 (20.0%)

Comparator group: PBSC 9 (60.0%), BM 5 (33.3%), PBSC+BM 1 (6.7%)

HSCT donor matching

Intervention group: "HLA identical"

Comparator group: "HLA identical"

Conditioning regimen: TBI + CY (BU + CY x1)

GvHD treatment: N/A

GvHD prophylaxis: intravenous CSA 3 mg kg⁻¹ d⁻¹ in divided doses beginning on the day before transplantation (day -1) and continued. MTX was administered intravenously at a dose of 15 mgm⁻² on day 1, and 10 mgm⁻² on days 3 and 6 after HSC transplantation. Patients were advanced to oral CSA once they could tolerate. In the absence of GvHD, the oral CSA dose was reduced by approximately 5% weekly, beginning on or near day 100, and therapy was usually discontinued for 6 months after transplantation or relapse.

Interventions	<p>Intervention arm: BM-derived MSCs: 0.3-15.3 x 10⁵ cells/kg, given intravenously over 30 minutes, 4 hours prior to HSCT</p> <p>Comparator arm: no MSCs</p> <p>Expansion protocol: FBS</p> <p>Prophylactic or therapeutic: prophylactic</p>
Outcomes	<p>Primary outcome: n/r</p> <p>Secondary outcomes: n/r</p>

Ning 2008 (Continued)

Reported outcomes

- Time to neutrophil/platelet engraftment
- Incidence of aGvHD and cGvHD
- Relapse
- Non-relapse mortality
- Overall survival
- Safety
- Rate of infection

Notes

Trial registration identifier: N/A

The planned enrolment was for 25 patients in each group. However, the trial was terminated early due to a higher median time to disease relapse in patients who received MSCs than in the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The authors stated that quote: "Patients were enrolled and allocated into two groups by using stratified random method, according to the enrolled time, age, disease types, stage and prognosis", but the method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	MSCs were derived from sibling donors; no MSCs were prepared for those in the control arm. No attempt at blinding was reported and no placebo was administered.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five randomised participants in the treatment arm were excluded but reasons were provided (failure to expand sufficient MSCs).
Selective reporting (reporting bias)	High risk	All outcomes reported in the methods were reported, but no protocol was available to fully assess selective reporting. The study aim was to quote: "investigate the potential benefits and side effects of cotransplanted MSCs" but no specific outcomes were detailed. The trial was terminated early due to a higher median time to disease relapse in patients who received MSCs than in the control group.
Other bias	Low risk	No other sources of bias were detected.

Osiris Protocol 260

Methods

Type of study: an open-label, multicentre, phase II dose-comparison randomised trial

Countries where study performed: USA (multicentre)

Dates of recruitment: April 2005 - June 2006

Osiris Protocol 260 (Continued)

Duration of follow-up: 90 days

Study funding: commercial sponsorship by Osiris Therapeutics, Inc.

Participants

Inclusion criteria

- Aged 18-70 years inclusive
- Acute GvHD grade II-IV requiring systemic steroid therapy
- Non-pregnant, non-breastfeeding, using adequate contraception.
- Received full or reduced intensity myeloablative regimens followed by an allogeneic HSCT using BM, PBSC or CB including DLI.
- Minimal renal and hepatic function
- Available for all specified assessments at the study site through study day 28
- Written informed consent

Exclusion criteria

- Treatment for aGvHD with ≥ 2 mg/kg methylprednisolone for >72 hours
- Use of any investigational agent within 30 days of randomisation
- Inadequate renal function

Number of participants randomised: 32 (16 MSC 8 x 10⁶ cells/kg; 16 MSC 2 x 10⁶ cells/kg)

Number of participants analysed: 31 (15 MSC 8 x 10⁶ cells/kg; 16 MSC 2 x 10⁶ cells/kg)

Age

Intervention group (8 x 10⁶ cells/kg): median 49 years (range 34 - 67 years)

Comparator group: (2 x 10⁶ cells/kg) median 53 years (range 42 - 67 years)

Gender

Intervention group: 67% male

Comparator group: 69% male

Disease

Intervention group: AML/MDS 8 (50.0%); ALL 3 (18.8%); NHL 2 (12.5%); CLL 1 (6.3%); MDS 1 (6.3%); MM 1 (6.3%)

Comparator group: AML/MDS 6 (37.5%); ALL 1 (6.3%); NHL 3 (18.8%); CLL 3 (18.8%); MMF 2 (12.5%); Hodgkin's disease 1 (6.3%)

Disease stage

Intervention group: n/r

Comparator group: n/r

GvHD involvement

Intervention group: Grade II 10 (66.7%); Grade III 4 (26.7%); Grade IV 1 (6.7%) (in 15 analysed participants)

Comparator group: Grade II 11 (68.8%); Grade III 3 (18.8%); Grade II 2 (12.5%)

Source of HSCT

Intervention group: PBSC 15 (100%) (in 15 analysed participants)

Comparator group: PBSC 15 (93.8%), BM 1 (6.2%)

Osiris Protocol 260 (Continued)

HSCT donor matching:

Intervention group: 9 matched related donors; 6 matched unrelated donors

Comparator group: 10 matched related donors; 6 matched unrelated donors

Conditioning regimen:

Intervention group: MAC 8; RIC 3; non-myeloablative 2, DLI 2

Comparator group: MAC 7, RIC 5, non-myeloablative 2, DLI 2

GvHD treatment: methylprednisolone 2 mg/kg intravenously or prednisone 2.5 mg/kg orally daily and then tapered as per institutional standard.

GvHD prophylaxis: CSA 6, tacrolimus 10, tacrolimus plus MMF or MTX 11

Interventions	<p>Intervention arm: BM-derived MSCs (Prochymal): 8 x 10⁶ cells/kg, given intravenously 3 days apart, the first infusion delivered within 24-48 hours of aGvHD diagnosis, with intravenous MTP 2 mg/kg or oral prednisone 2.5 mg/kg daily and then tapered as per institutional standard.</p> <p>Comparator arm: BM-derived MSCs (Prochymal): 2 x 10⁶ cells/kg, given intravenously 3 days apart, the first infusion delivered within 24-48 hours of aGvHD diagnosis, with intravenous MTP 2 mg/kg or oral prednisone 2.5 mg/kg daily and then tapered as per institutional standard.</p> <p>Expansion protocol: FBS</p> <p>Prophylactic or therapeutic: therapeutic</p>	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">• Overall response by study day 28• Incidence rate of different adverse events at 2 years <p>Secondary outcomes</p> <ul style="list-style-type: none">• Partial response or improvement of GvHD by day 28 in one or more organs• Time to best response of GvHD• Time to improvement of GvHD in one or more organs• Survival through to day 90	
Notes	<p>Trial registration identifier: NCT00136903</p>	
<p><i>Risk of bias</i></p>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised using a stratified block design but the method of random sequence allocation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label trial; no blinding of participants or personnel was attempted.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an open-label trial. No blinding of outcome assessors was reported.

Osiris Protocol 260 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	There was one withdrawal in the high cell dose group which was explained as withdrawal of consent.
Selective reporting (reporting bias)	Low risk	All outcomes defined in the protocol were reported in the paper.
Other bias	Low risk	The study appears to be free of other sources of bias.

Osiris Protocol 265

Methods	<p>Type of study: a phase 3, double-blind, randomised, placebo-controlled trial</p> <p>Countries where study performed: USA/Australia/Canada (multicentre)</p> <p>Dates of recruitment: n/r</p> <p>Duration of follow-up: 90 days (safety: 1 year)</p> <p>Study funding: Commercial sponsorship by Osiris Therapeutics, Inc.</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • 18-70 years inclusive • Recipient of HSCT (BM, PBSC or CB) or DLI • Newly diagnosed grade B-D GvHD • Treated with corticosteroids within 72 hours of onset of aGvHD • Adequate renal function • Minimum Karnofsky Performance Level of at least 30 at time of study entry • Written informed consent <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Previous treatment with systemic immunosuppressive therapy for aGvHD • Relevant underlying medical/psychiatric conditions • Receiving no other investigational agents • Allergy to bovine/porcine products or DMSO • Recipient of transplant for solid tumour disease • Requiring more than 2L/minute O₂ • Renal dopamine dose >1-3 mcg/kg/minute <p>Number of participants randomised: n/r</p> <p>Number of participants analysed: 192 (numbers per treatment arm n/r)</p> <p>Age</p> <p>Intervention group: n/r</p> <p>Comparator group: n/r</p> <p>Gender</p> <p>Intervention group: n/r</p> <p>Comparator group: n/r</p> <p>Disease</p>

Osiris Protocol 265 (Continued)

Intervention group: n/r

Comparator group: n/r

Disease stage

Intervention group: aGvHD grade B-D

Comparator group: aGvHD grade B-D

GvHD involvement

All participants had aGvHD

HSCT donor matching: n/r

Source of HSCT: BM or PBSC or CB or DLI (frequencies not reported)

Conditioning regimen: MTP

GvHD treatment: n/r

GvHD prophylaxis: n/r

Interventions	<p>Intervention arm: BM-derived MSCs (Prochymal): 2 x 10⁶ cells/kg, given intravenously, 2 infusions per week for the first two weeks, then weekly for two weeks (total 6 infusions over four weeks).</p> <p>Comparator arm: placebo (excipient, less cells), given intravenously, 2 infusions per week for the first two weeks, then weekly for two weeks (total 6 infusions over four weeks).</p> <p>Expansion protocol: FBS</p> <p>Prophylactic or therapeutic: therapeutic</p>	
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none">Complete response, followed by 28 days of maintenance of a clinically meaningful response without requirement for an increase in corticosteroid dose, did not require second line therapy and survived 90 days. <p>Secondary outcomes</p> <ul style="list-style-type: none">Overall responseInduction of a two grade decrease in GvHD and maintenanceInduction of a CR lasting ≥14 days,Time to CRIncidence of CR per organTotal steroid dose through day 90Incidence of steroid/infectious complications	
Notes	<p>Trial registration identifier: NCT00562497</p>	
<p>Risk of bias</p>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.

Osiris Protocol 265 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial was described as "double-blind" and a placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was blinded until data analysis at day 90 post first infusion.
Incomplete outcome data (attrition bias) All outcomes	High risk	The number of participants randomised and analysed in each treatment arm was not reported.
Selective reporting (reporting bias)	High risk	Only very limited summary data were reported in a press release.
Other bias	High risk	Results of this trial have not been published and there is no indication that they will be published in the future.

Osiris Protocol 280

Methods	<p>Type of study: a phase 3, multicentre, double-blind, randomised, placebo-controlled trial.</p> <p>Countries where study performed: USA, Canada, Australia, Germany, Italy, Spain, United Kingdom (72 sites)</p> <p>Dates of recruitment: August 2006 - May 2009</p> <p>Duration of follow-up: 100 days (survival at 180 days)</p> <p>Study funding: commercial sponsorship by Osiris Therapeutics, Inc.</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Males and females, aged 6 months to 70 years inclusive Grades B-D acute GvHD that had failed to respond to steroid treatment, and was secondary to allogeneic HSCT (BM, PBSC or CB cells) or DLI Minimum Karnofsky Performance Status score of at least 30 (adults) or minimum Lansky Play Scale score of 30 (paediatrics) <p>Exclusion criteria</p> <ul style="list-style-type: none"> Primary treatment with agents other than corticosteroids <p>Number of participants randomised: 260 (173 MSC, 87 no MSC)</p> <p>Number of participants analysed: 260 (173 MSC, 87 no MSC)</p> <p>Age: Mean 42.3 (SD 17.2) years</p> <p>Gender: n/r</p> <p>Disease</p> <p>Intervention group: AML 49 (28.3%) (most frequent)</p> <p>Comparator group: AML 23 (26.4%) (most frequent)</p> <p>Disease stage: n/r</p>

Osiris Protocol 280 (Continued)

GvHD involvement

Intervention group: aGvHD Grade B 38 (22.0%); Grade C 88 (50.9%); Grade D 47 (27.2%). Two organ involvement: 57 (32.9%)

Comparator group: aGvHD Grade B 23(26.4%); Grade C 50 (57.5%); Grade D 14 (16.1%). Two organ involvement: 40 (46.0%)

Source of HSCT

Intervention group: PBSC 135 (78.0%), BM/CB or DLI 38 (22.0%)

Comparator group: PBSC 62 (71.3%), BM/CB or DLI 25 (28.7%)

HSCT donor matching: n/r

Conditioning regimen

Intervention group: MAC 113 (65.3%)

Comparator group: MAC 64 (73.6%)

GvHD treatment: n/r (quote: "GVHD therapies administered as per institutional guidelines")

GvHD prophylaxis: quote: "Standard of care"

Interventions	<p>Intervention arm: BM-derived MSCs (Prochymal): 2×10^6 cells/kg, given intravenously, 8 infusions by study day 28, administered at least 3 days apart.</p> <p>Comparator arm: placebo infusion, given intravenously, 8 infusions by study day 28, administered at least 3 days apart.</p> <p>Expansion protocol: n/r</p> <p>Prophylactic or therapeutic: therapeutic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Complete response of ≥ 28 days duration within 100 days post-first infusion in the ITT population <p>Secondary outcomes</p> <ul style="list-style-type: none"> Survival at 100 (+/-3 days) post infusion Survival at 180 (+/-7) days post infusion Cumulative steroid usage <p>Additional efficacy variables 'of interest'</p> <ul style="list-style-type: none"> Incidence of overall response (CR+PR) by organ at days 28 and 100 Time to CR Durability of organ response Change from baseline in QoL and Karnofsky/Lansky Performance Status assessments; Additional exploratory analyses including induction, duration and time to different definitions of response
Notes	Trial registration identifier: NCT00366145
Risk of bias	
Bias	Authors' judgement Support for judgement

Osiris Protocol 280 (Continued)

Random sequence generation (selection bias)	Low risk	Patients were randomised in a blinded fashion using a central Interactive Voice Response System (IVRS). Patients were stratified and balanced by grades of GvHD.
Allocation concealment (selection bias)	Low risk	Only designated technicians in the Central Processing Laboratory at the study sites were unblinded to treatment, and designated cell processing technicians prepared both the Prochymal and placebo infusions. The Prochymal and placebo infusions were prepared in identical infusion bags and infused with similarly masked infusion tubing.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The treatment each patient received was not disclosed to the investigator, study site, personnel, patient, sponsor or the contracted clinical research organisation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The treatment each patient received was not disclosed to the investigator, study site, personnel, patient, sponsor or the contracted clinical research organisation (except for the unblinded analysis team servicing the data safety monitoring board and the unblinded monitor). quote: "The database lock occurred following assignment of all disposition codes, finalisation of the statistical analysis plan, signing off of outstanding queries, database audit completion, and resolution of issues raised during the blinded review of data. Complete study unblinding occurred following database lock and signed authorisation from the sponsor."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis of a modified ITT (mITT) population and safety population included all patients who had been randomised and received at least 21 doses of investigational agent. The per-protocol population included mITT patients who were compliant to the treatment plan and adherent to key inclusion/exclusion criteria. Reasons for withdrawals and exclusions were detailed.
Selective reporting (reporting bias)	High risk	Results were only published in abstract form and via press releases by the trial sponsors. Detailed results were obtained from licensing application documents published by the Australian Government Therapeutic Goods Administration; however not all outcome results were reported therein.
Other bias	Unclear risk	Data have been obtained from the Australian Government Therapeutic Goods Administration, and not directly from Osiris.

Wu 2013

Methods	<p>Type of study: a randomised controlled trial</p> <p>Countries where study performed: China</p> <p>Dates of recruitment: n/r</p> <p>Duration of follow-up: median 16.5 months (range 8 - 27 months)</p> <p>Study funding: supported by the Ministry of Economic Affairs in Taiwan and grants from the China Medical University Hospital and Chung Shan Medical University Hospital</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Children with high-risk leukaemia (ALL with cytogenetic abnormalities indicating poor prognosis, in second remission, or with MDS) but lacking HLA-matched siblings or unrelated donors Parental written informed consent

Wu 2013 (Continued)

Exclusion criteria

- Patients receiving two or more units of CB

Number of participants randomised: 20 (8 MSC; 12 no MSC)

Number of participants analysed: 20 (8 MSC; 12 no MSC)

Age

Intervention group: median 9.8 years (range 3.2 - 12.1 years)

Comparator group: median 8.5 years (range 3.6 - 13.1 years)

Gender

Intervention group: 63% male

Comparator group: 50% male

Disease

Intervention group: AML 5 (62.5%); ALL 3 (37.5%)

Comparator group: AML 7 (58.3%), ALL 5 (41.7%)

Disease stage

Intervention group: AML in 2nd remission 2 (25.0%); ALL in 2nd remission 1 (12.5%); AML with MDS 2 (25.0%), ALL with Ph 2 (25.0%), AML with monosomy 7 1 (12.5%)

Comparator group: ALL in 2nd remission 3 (25.0%), AML in 2nd remission 3 (25.0%), AML in 1st remission 2 (16.7%), ALL with Ph 2 (16.7%), AML with MDS 2 (16.7%)

GvHD involvement

Intervention group: no GvHD 4 (50.0%); Grade I 3 (37.5%); Grade II 1 (12.5%)

Comparator group: no GvHD 4 (33.3%); Grade I 5 (41.7%); Grade II 2 (16.7%); Grade III 1 (8.3%)

Source of HSCT: CB

HSCT donor matching

Intervention group: matched loci: 3/6 (2); 4/6 (4); 5/6 (2)

Comparator group: matched loci: 4/6 (6); 5/6 (6)

Conditioning regimen: ALL: CY 60 mg/kg/day intravenously for 2 days, etoposide 30 mg/kg intravenously for 1 day, TBI 200 cGy twice a day for 3 days. Patients with AML: BU 1 mg/kg intravenously every 6 hours for 4 days, and CY 60 mg/kg/day intravenously for 2 days.

GvHD treatment: N/A

GvHD prophylaxis: Intravenous or oral CSA and intravenous MTP. All patients received rabbit thy-moglobulin 2.5 mg/kg/day intravenously for 4 days.

Interventions

Intervention arm: UC Wharton's Jelly-derived MSCs: median 7.19 (range 2.44 to 10.12) x 10⁶ cells/kg In-fused during 30 minutes through central venous line 4oursh prior to CB infusion.

Comparator arm: no MSC

Expansion protocol: α-MEM with 10% FBS

Prophylactic or therapeutic: prophylactic

Wu 2013 (Continued)

Outcomes	Primary outcome: n/r Secondary outcomes: n/r Reported outcomes <ul style="list-style-type: none">• Safety (tolerance, infusion-related toxicities, ectopic tissue formation)• Infection• Engraftment (platelets/neutrophils)• aGvHD• cGvHD• Relapse• Mortality	
Notes	Trial registration identifier: N/A	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants or personnel was not reported; no placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals were reported; individual patient data were provided.
Selective reporting (reporting bias)	Unclear risk	No protocol was described or identified to allow assessment of selective reporting bias.
Other bias	Low risk	No other sources of bias were detected.

Zheng 2015

Methods	Type of study: a prospective multicentre randomised controlled trial Countries where study performed: China Dates of recruitment: July 2010 - December 2014 Duration of follow-up: mean 13.4 months (MSC); mean 23.6 months (no MSC) Study funding: n/r
Participants	Inclusion criteria

Mesenchymal stromal cells as treatment or prophylaxis for acute or chronic graft-versus-host disease in haematopoietic stem cell transplant (HSCT) recipients with a haematological condition (Review)

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Zheng 2015 (Continued)

- Extensive cGvHD with skin and/or liver damage developed after allogeneic HSCT
- Chronic GvHD that do not response to conventional immunosuppressant treatment for two months
- Karnofsky Performance Status ≥ 30

Exclusion criteria

- Extensive cGvHD without skin or liver damage
- Other acute severe complications
- Pregnancy/lactation
- Disease relapse
- Non-haematological malignancy

Number of participants randomised: 40 (30 MSC; 10 no MSC)

Number of participants analysed: 40 (30 MSC; 10 no MSC)

Age: n/r

Gender: n/r

Disease: n/r

Disease stage: n/r

GvHD involvement: n/r

Source of HSCT: n/r

HSCT donor matching: n/r

Conditioning regimen: n/r

GvHD treatment: n/r

GvHD prophylaxis: n/r

Interventions	<p>Intervention arm: MHC-mismatched MSCs: $1-4 \times 10^7$ weekly, total $4.8-16 \times 10^7$ over four weeks</p> <p>Comparator arm: no MSC</p> <p>Expansion protocol: n/r</p> <p>Prophylactic or therapeutic: therapeutic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Number of patients with complete and partial response <p>Secondary outcomes</p> <ul style="list-style-type: none"> • One-year survival rate • Disease relapse at 2 years • Quality of life at 2 years <p>Reported outcomes</p> <ul style="list-style-type: none"> • Improvement of cGvHD signs/symptoms • Relapse of haematological malignancies • Overall survival • Progress-free survival • T cell subsets

Zheng 2015 (Continued)

Notes

Trial registration identifier: NCT01526850

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants or personnel was not reported; no placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors was not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals or exclusions were reported.
Selective reporting (reporting bias)	High risk	Relapse of haematological malignancies and progress-free survival were defined as outcomes in the methods but results were not reported. Outcomes were measured at 1, 2, 3, 6, 12 months post-MSCs but only results at long-term follow-up reported.
Other bias	Unclear risk	In this conference abstract there was insufficient information to assess any other potential sources of risk of bias.

α-MEM: minimum essential medium with α modification; **aGvHD:** acute graft-versus-host disease; **ALL:** acute lymphoblastic leukaemia; **AML:** acute myeloid leukaemia; **Ara-C:** arabinosylcytosine; **ATG:** antithymocyte globulin; **BM:** bone marrow; **BU:** busulphan; **CA:** cytosine arabinoside; **CB:** cord blood; **CCNU:** chlorethyl cyclohexyl nitrosourea; **cGvHD:** chronic graft-versus-host disease; **CLL:** chronic lymphoid leukaemia; **CML:** chronic myeloid leukaemia; **CMV:** cytomegalovirus; **CP:** chronic phase; **CP2:** second chronic phase; **CR:** complete remission; **CR1:** complete first remission; **CR2:** complete second remission; **CSA:** cyclosporine A; **CY:** cyclophosphamide; **DLI:** donor lymphocyte infusion; **DMEM:** Dulbecco's Modified Eagle's medium; **DMSO:** Dimethyl sulphoxide; **FBS:** fetal bovine serum; **HLA:** human leukocyte antigen; **HSCT:** haematopoietic stem cell transplant; **ITT:** intention-to-treat; **KPS:** Karnofsky Performance Status; **MAC:** myeloablative conditioning; **MDS:** myelodysplastic syndrome; **MF:** myelofibrosis; **MM:** multiple myeloma; **MMF:** mycophenolate mofetil; **MSC:** mesenchymal stromal cells; **MTP:** methylprednisolone; **MTX:** methotrexate; **N/A:** not applicable; **n/r:** not reported; **NHL:** non-Hodgkins lymphoma; **NK cells:** natural killer cells; **PB:** peripheral blood; **PBSC:** peripheral blood stem cells; **Ph:** Philadelphia chromosome; **PL:** platelet lysate; **PR:** partial remission; **QoL:** quality of life; **RAS:** refractory anaemia with ringed sideroblasts; **RIC:** reduced intensity conditioning; **SD:** standard deviation; **TBI:** total body irradiation; **UC:** umbilical cord

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Batorov 2015	Non-randomised treatment allocation
Boome 2012	Single-arm trial
EUCTR2005-003674-14-ES	Single-arm trial

Study	Reason for exclusion
EUCTR2008-007869-23-IT	Single-arm trial
Gonzalo-Daganzo 2009	Single-arm trial
Han 2014	Non-randomised treatment allocation
Hou 2010	Non-randomised treatment allocation
Ilic 2014	Pre-clinical trial
Introna 2014	Single-arm trial
JPRN-C000000423	Single-arm trial
Kozlov 2009	Single-arm trial
Lazarus 2005	Single-arm trial
Lee 2007	Single-arm trial
Lee 2013	Non-randomised historic controls
Macmillan 2009	Non-randomised treatment allocation
Maziarz 2015	Non-randomised treatment allocation
Molnar 2018	Single-arm trial
NCT00081055	Withdrawn prior to enrolment
NCT01129739	Incorrect patient population (no HSCT given)
NCT01182662	Incorrect patient population (no HSCT given)
NCT01854567	Incorrect intervention (one mesenchymal precursor cell expanded cord unit and one unexpanded cord unit versus two unexpanded cord blood units)
NCT02240992	Incorrect intervention (MSCs compared with MSCs plus peripheral blood stem cells)
Ozawa 2011	Single-arm trial
Perez-Simon 2011	Single-arm trial
Resnick 2009	Single arm trial
Xiao 2016	Single arm trial
Xiong 2014	Incorrect intervention (MSCs compared with MSCs combined with cord blood)
Zhao 2015	Non-randomised treatment allocation

HSCT: haematopoietic stem cell transplant; **MSC:** mesenchymal stromal cells

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ghavamzadeh 2017

Methods	<p>Type of study: a two-arm trial (unclear whether randomised)</p> <p>Countries where study performed: Iran</p> <p>Dates of recruitment: January 2010 to January 2015</p> <p>Duration of follow-up: 3 years</p> <p>Study funding: n/r</p>
Participants	<p>Inclusion criteria: beta-thalassaemia major patients requiring HSCT</p> <p>Exclusion criteria: n/r</p> <p>Number of participants randomised: n/r (70 recruited)</p> <p>Number of participants analysed: 70 (41 MSC, 29 no MSC)</p> <p>Age: n/r</p> <p>Gender: n/r</p> <p>Disease Intervention group: thalassaemia major Comparator group: thalassaemia major</p> <p>Disease stage Intervention group: n/r Comparator group: n/r</p> <p>GvHD involvement: N/A</p> <p>Source of HSCT: n/r</p> <p>HSCT donor matching Intervention group: "HLA identical siblings" Comparator group: "HLA identical siblings"</p> <p>Conditioning regimen: CY or fludarabine-based regimen</p> <p>GvHD treatment: N/A</p>
Interventions	<p>Intervention arm: MSCs: $1.0-2.0 \times 10^6$ cells/kg</p> <p>Comparator arm: no MSCs</p> <p>Expansion protocol: PL</p> <p>Prophylactic or therapeutic: prophylactic</p>
Outcomes	<p>Primary outcome: n/r</p> <p>Secondary outcomes: n/r</p> <p>Reported outcomes</p>

Ghavamzadeh 2017 (Continued)

- Engraftment
- Incidence of aGvHD
- Incidence of cGvHD
- Overall survival at 3 years
- Thalassaemia-free survival at 3 years
- Transplant-related mortality

Notes

This study was identified from the final search update (6 December 2018) and will be incorporated in future updates of this review. subject to confirmation of randomisation.

Xiang 2017
Methods

Type of study: a two-arm randomised trial

Countries where study performed: China

Dates of recruitment: n/r

Duration of follow-up: 6 months (1 year survival)

Study funding: The Scientific and Technological Achievements of Nanyang City, No. 16058080

Participants

Inclusion criteria: children with acute lymphoblastic leukaemia; recipients of HSCT

Exclusion criteria: n/r

Number of participants randomised: 64 (32 MSC, 32 no MSC)

Number of participants analysed: 64 (32 MSC, 32 no MSC)

Age:

n/r (children)

Gender: n/r

Disease

Intervention group: ALL

Comparator group: ALL

Disease stage

Intervention group: n/r

Comparator group: n/r

GvHD involvement: N/A

Source of HSCT: n/r

HSCT donor matching: n/r

Conditioning regimen: n/r

GvHD treatment: N/A

Interventions

Intervention arm: human umbilical cord MSCs (dose n/r)

Comparator arm: no MSCs

Xiang 2017 (Continued)

	Expansion protocol: n/r Prophylactic or therapeutic: prophylactic
Outcomes	Primary outcome: n/r Secondary outcomes: n/r Reported outcomes <ul style="list-style-type: none"> Granulocyte implantation rate HSCT implantation rate Platelet remodelling rate Cumulative recurrence rate Incidence of cGvHD Incidence of CMV One-year survival rate Serum immunoglobulin and T-lymphocyte levels
Notes	Published in Chinese (data above extracted from English abstract). This study was identified from the final search update (6 December 2018) and will be translated and incorporated in future updates of this review.

aGvHD: acute graft-versus-host disease; **cGvHD:** chronic graft-versus-host disease; **ALL:** acute lymphoblastic leukaemia; **CMV:** cytomegalovirus; **CY:** cyclophosphamide; **HLA:** human leukocyte antigen; **HSCT:** haematopoietic stem cell transplant; **MSC:** mesenchymal stromal cells; **N/A:** not applicable; **n/r:** not reported; **PL:** platelet lysate

Characteristics of ongoing studies [ordered by study ID]

ACTRN12608000129381

Trial name or title	Cotransplantation of mesenchymal stem cells with nonmyeloablative haploidentical peripheral blood stem cells without T cells deleted for high-risk acute leukemia: to reduce the severity of graft-versus-host disease and relapse
Methods	Type of study: a retrospectively registered, parallel, open-label, phase II randomised controlled trial Country where study performed: China Intended duration of follow-up: 3 years
Participants	Inclusion criteria <ul style="list-style-type: none"> High risk leukaemia patients Aged 9-60 years Both males and females Exclusion criteria <ul style="list-style-type: none"> Blast cells over 50% in bone marrow after chemotherapy
Interventions	Intervention arm: MSCs administrated by intra-bone marrow injection into iliac bones 30 minutes before haematopoietic stem cell infusion at day 0 Comparator arm: placebo (unspecified) Prophylactic or therapeutic: prophylactic

ACTRN12608000129381 (Continued)

Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Transplant-related mortality, including conditioning complications and severe infection at 1 year • Incidence of GvHD including aGvHD and cGvHD at 1 year <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Overall survival at 3 years • Leukaemia relapse rates at 3 years
Starting date	March 2008
Contact information	<p>Contact information:</p> <p>Kaixun Hu (Phone: +86 01066947129; Email: hukaixun@sohu.com)</p> <p>Huisheng Ai (Phone: +86 01066947126; Email: aihuisheng@sohu.com)</p>
Notes	<p>Date first received: 11 February 2008</p> <p>Planned enrolment: 40</p> <p>Estimated completion date: n/r</p> <p>Trial status: we have been unable to establish the current status of this trial and have not identified any associated publications.</p>

ChiCTR-IIR-16007806

Trial name or title	Clinical study of umbilical cord-derived mesenchymal stem cells in the prophylaxis of chronic graft-versus-host disease after HLA-haploidentical stem cell transplantation--multicenter, randomized parallel controlled, double-blind trial
Methods	<p>Type of study: a prospectively registered, multicentre, parallel, phase II randomised controlled trial</p> <p>Countries where study performed: China</p> <p>Intended duration of follow-up: 2 years</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • HLA-haploidentical HSCT patients without GvHD • Age between 18 to 60 years • KPS score > 60 • No serious organ dysfunction • Expected survival > 3 months <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Serious organ dysfunction • Requirement for other cancer treatment • Presence of clinical signs of brain dysfunction or severe mental illness which cannot comply with the study protocol • Cannot complete scheduled follow-up • Cannot guarantee the completion of the treatment plan and the necessary follow-up observation
Interventions	Intervention arm: infusion of umbilical cord-derived MSCs 1×10^6 /kg per 15 days, total 4 times

Mesenchymal stromal cells as treatment or prophylaxis for acute or chronic graft-versus-host disease in haematopoietic stem cell transplant (HSCT) recipients with a haematological condition (Review)

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ChiCTR-IIR-16007806 (Continued)

Comparator arm: placebo (same volume normal saline)

Prophylactic or therapeutic: prophylactic

Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Chronic GvHD <p>Secondary outcomes</p> <ul style="list-style-type: none"> Relapse Overall survival Disease-free survival Security Lymphocyte subset
Starting date	April 2016
Contact information	<p>Contact information:</p> <p>Lei Gao (Phone: +86 13228689635; Email: gaolei7765@163.com)</p> <p>Xi Zhang (Phone: +86 13808310064; Email: zhangxxi@sina.com)</p>
Notes	<p>Planned enrolment: 156</p> <p>Estimated completion date: n/r</p> <p>Trial status: recruiting</p>

ChiCTR-INR-16008399

Trial name or title	Cotransplantation of haploidentical peripheral blood stem cells and mesenchymal stem cells for acute leukemia: a randomized, controlled clinical study
Methods	<p>Type of study: a prospectively registered, parallel, randomised controlled trial</p> <p>Countries where study performed: China</p> <p>Intended duration of follow-up: 3 years</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Acute leukaemia patients (including AML and ANML) at first complete remission before transplantation HLA matching of the donor and the patients was haploidentical Patients received allogeneic haematopoietic stem cell transplantation in our hospital from January 2016 to December 2019 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Patients aged 14~55 years old Patients do not achieve remission Patients with heart, lung or kidney dysfunction Patients with mental disorders Pregnancy patients with leukaemia

ChiCTR-INR-16008399 (Continued)

Interventions	<p>Intervention arm 1: cotransplantation of haploidentical peripheral blood stem cells and mesenchymal stem cells (d0)</p> <p>Intervention arm 2: cotransplantation of haploidentical peripheral blood stem cells and mesenchymal stem cells (d+30)</p> <p>Comparator arm: control (haploidentical peripheral blood stem cell transplantation)</p> <p>Prophylactic or therapeutic: prophylactic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Overall survival at 1 and 3 years after transplantation Rate of relapse at 1 and 3 years after transplantation <p>Secondary outcomes</p> <ul style="list-style-type: none"> Rate of graft at 1 month Rate of aGvHD and cGvHD within 100 days and 100 days after transplantation
Starting date	May 2016
Contact information	<p>Contact information:</p> <p>Xiaoning Wang (Phone: +86 18991232608; Email: wangxn99@163.com)</p> <p>Pengcheng He (Phone: +86 18991232609; Email: hepc@163.com)</p>
Notes	<p>Planned enrolment: 36</p> <p>Estimated completion date: patients recruited until December 2019.</p> <p>Trial status: recruiting</p>

EUCTR2008-005594-35-BE

Trial name or title	Randomized double-blind study of mesenchymal stem cells (MSC) in patients undergoing matched unrelated allogeneic bone marrow or peripheral blood stem cell transplantation- A European multicentre study
Methods	<p>Type of study: a multicentre, phase III, double-blind, randomised controlled trial</p> <p>Country where study performed: Belgium</p> <p>Intended duration of follow-up: n/r</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Informed consent Patients/participants are required to meet the following inclusion criteria: a) haematological disorders of the following types (ALL: patients with acute lymphoblastic leukaemia in CR (<5% blasts in marrow) up to and including third remission (excluding relapse), AML: patients with acute myelocytic leukaemia in remission, CML: patients with chronic myelocytic leukaemia who are in the chronic phase of the disease, severe aplastic anaemia, haemoglobinopathies (thalassaemia major), inborn errors of metabolism, MDS. b) patients may have undergone myeloablative or reduced intensity conditioning regimen. c) use of anti-thymocytes globulin (ATG) during conditioning, according to the routine at each centre. Both arms must be treated identically at each centre. Adequate cardiac function. Left ventricular ejection fraction or megascan or echocardiography must be at least 40% of predicted.

EUCTR2008-005594-35-BE (Continued)

- Adequate pulmonary function as defined as no severe or symptomatic restrictive or obstructive lung disease. FEV-1 >50% of predicted and DLCO > 50% of predicted.
- Female patients are non-pregnant
- Patients must be HIV-1 and -2 antibody, HIV -1 antigen and hepatitis A, B and C seronegatives
- Patients must have a Karnofsky score of =70
- Patients must have an HLA-A, -B and -DRβ1 identical stem cell donor (HLA typing according to the routine at each centre)
- Immunosuppression should consist of cyclosporine or tacrolimus combined with four doses of methotrexate. Methotrexate is given on day+1, 15 mg/m² and 10 mg/m² on days +3, +6 and +11 after transplantation. Cyclosporine or tacrolimus dose is according to the routines at each centre. Because acute GvHD is a primary endpoint, no other immunosuppression than cyclosporine combined with methotrexate will be allowed.

Exclusion criteria

- Haematologic malignancies, of the following types: a) ALL patients in relapse as defined by > 5% blasts in the marrow and/or circulating blasts in the peripheral blood, b) AML patients in relapse as defined by > 5% blasts in the marrow, c) AML/ALL CR4 or later, d) CML in accelerated phase or blast crisis, e) MDS > RAEB II.
- Patient has active alcohol or substance abuse
- Patient has a medical condition, which, in the opinion of the clinical investigator, would interfere with the evaluation of the patient
- Patient needing haematopoietic stem cell transplantation within three weeks
- Patient with a history of hyper-sensitivity to penicillin

Interventions	<p>Intervention arm: intravenous infusion of MSCs (dose/schedule not specified)</p> <p>Comparator arm: placebo (unspecified)</p> <p>Prophylactic or therapeutic: prophylactic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • GvHD incidence (acute grade II-IV GvHD) will be used as measure of efficacy <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Determination of time to neutrophil engraftment (> 0.5 x 10E9/L) • Determination of time to platelet engraftment (> 30 x 10E9/L) • Platelet level at day 30 post transplant • Transfusions during first 30 days • Incidence of chronic GvHD • Treatment-related mortality (causes of death) • Overall relapse rate • Survival • Disease-free survival
Starting date	n/r
Contact information	Contact information: Centre Hospitalier Universitaire De Liège, Rue du Sart-Tilman 35, 4031 Angleur, Belgium
Notes	<p>Planned enrolment: 172</p> <p>Estimated completion date: n/r</p> <p>Trial status: ongoing (confirmed with trial investigators on 26 October 2017)</p>

EUCTR2009-014980-38-BE

Trial name or title	Co-transplantation of mesenchymal stem cells and HLA-mismatched allogeneic hematopoietic cells after reduced-intensity conditioning: a phase II randomized double-blind study
Methods	<p>Type of study: a phase II, double-blind, randomised controlled trial</p> <p>Countries where study performed: Belgium</p> <p>Intended duration of follow-up: 2 years</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Haematological malignancies confirmed histologically and not rapidly progressing (see E1.1) • Theoretical indication for a standard allo-transplant, but not feasible because: age > 55 years; unacceptable end organ performance; patient's refusal • Indication for a standard auto-transplant: perform mini-allotransplantation 2-6 months after standard autotransplant • Male or female; fertile female patients must use a reliable contraception method • Age 75 years or below • Informed consent given by patient or his/her guardian if of minor age • One or two HLA mismatches as described in the protocol <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Any condition not fulfilling inclusion criteria • HIV positive • Terminal organ failure, except for renal failure (dialysis acceptable): Cardiac: Symptomatic coronary artery disease or other cardiac failure requiring therapy; ejection fraction < 35%; uncontrolled arrhythmia, uncontrolled hypertension; pulmonary: DLCO < 35% and/or receiving supplementary continuous oxygen; hepatic: fulminant liver failure, cirrhosis of the liver with evidence of portal hypertension, alcoholic hepatitis, oesophageal varices, a history of bleeding oesophageal varices, hepatic encephalopathy, uncorrectable hepatic synthetic dysfunction evinced by prolongation of the prothrombin time, ascites related to portal hypertension, bacterial or fungal liver abscess, biliary obstruction, chronic viral hepatitis with total serum bilirubin > 3 mg/dL, and symptomatic biliary disease • Uncontrolled infection, arrhythmia or hypertension • Previous radiation therapy precluding the use of 2 Gy TBI • 10/10 HLA-A, -B, -C, DRB1 and DQB1 allele-matched donor fit to/willing to donate PBSC
Interventions	<p>Intervention arm: intravenous infusion of 1.5×10^6 MSC/kg to 3.0×10^6 MSC/kg</p> <p>Comparator arm: placebo (unspecified)</p> <p>Prophylactic or therapeutic: prophylactic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Overall survival at 1 year <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Incidences of grade II-IV and grade III-IV acute GvHD disease • Cumulative incidence of non-relapse mortality at days 100, 365 and 730. • Incidence of extensive chronic GvHD at day 365 • Incidence of graft rejection • Cumulative incidence of relapse at days 365 and 730 • Incidence of progression-free survival at days 365 and 730

EUCTR2009-014980-38-BE (Continued)

- Incidence of infections at day 100
- Quality and timing of immunologic reconstitution in each arm
- To detect MSC of MSC donor origin in recipient marrow after haematopoietic cell transplantation (HCT) in patients given MSC (ULg-CHU patients only)
- To assess the proportion of patients with measurable disease at HCT who achieve a complete response in each arm
- To compare the number of absolute donor T cells on day 28 after in each arm
- To compare these endpoints in patients conditioned with either fludarabine and 2 Gy TBI or fludarabine-busulphan-ATG

Starting date	n/r
Contact information	Contact information: Yves Beguin, Centre Hospitalier Universitaire De Liège, Belgium (Phone: +32 043667201)
Notes	<p>Planned enrolment: 120</p> <p>Estimated completion date: n/r</p> <p>Trial status: ongoing (confirmed with trial investigators on 26 October 2017)</p>

EUCTR2011-003237-33-NL

Trial name or title	Treatment of severe acute GVHD after allogeneic hematopoietic stem cell transplantation with steroids versus MSC and steroids. A prospective double-blind placebo-controlled randomized phase III trial
Methods	<p>Type of study: a multicentre, prospective, double-blind, parallel, placebo-controlled randomised phase III trial</p> <p>Countries where study performed: the Netherlands</p> <p>Intended duration of follow-up: 10 years</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Any age • Previously treated with allo-SCT/ DLI • Grade II-IV aGVHD involving gut and/or liver, confirmed by histology of involved tissues, however, the first infusion of MSC can be given without final histological confirmation • WHO performance 0-3 • Negative pregnancy test (if applicable) • Patients must be willing and capable to use adequate contraception during therapy (if applicable) • Written Informed consent by the patient and/or parent(s) or legal guardian(s) <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Patients with active, uncontrolled infection • Rapid progressive haematological malignancy • Patients pre-treated with prednisolone > 1 mg/kg for GVHD, for more than 72 hours prior to randomisation/application of MSC • Known uncontrolled toxicity for DMSO • Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, cancer, etc.)

EUCTR2011-003237-33-NL (Continued)

- Any psychological, familial, sociological and/or geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Interventions	<p>Intervention arm: Intravenous infusion of 1×10^6 to 5×10^6 MSCs</p> <p>Comparator arm: Placebo (unspecified)</p> <p>Prophylactic or therapeutic: therapeutic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Proportion of patients in each treatment arm who experience a CR-GvHD or PR-GvHD at day 57 after randomisation, without treatment failure (initiation of secondary treatment; progression/relapse, or death) <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Proportion of patients in each treatment arm who experience a CR-GvHD or PR-GvHD at indicated days after initiation of study-treatment, without treatment failure (initiation of secondary treatment, progression/relapse, or death) Time to CR-GvHD or PR-GvHD Amount of immune suppression at indicated days (and cumulative exposure of steroid till above mentioned time points) Adverse events The (immunological) phenotype before and after application of MSC of responders and non-responders in both groups at different sites including the validation of a defined predictive early phenotype The immunological genotype of responders and non-responders as well as donors in both groups Quality of life at indicated days Cost-effectiveness as determined by hospital admission days from randomisation until day 57 calculated against the price of MSC Relapse of the underlying disease (e.g. haematological malignancy) Incidence and severity of chronic GvHD Progression-free survival, defined as time from randomisation until progression or relapse (of the underlying disease), or death whichever the cause Overall survival, defined as time from randomisation until death whichever the cause. Patients still alive at the date of last contact, will be censored
Starting date	December 2013
Contact information	Contact information: Prof. Dr. J Kuball, HOVON Data Center (Phone: +31 107041560; Email: hd-c@erasmusmc.nl)
Notes	<p>Planned enrolment: 200</p> <p>Estimated completion date: December 2023</p> <p>Trial status: ongoing</p>

EUCTR2012-004915-30-NL

Trial name or title	Treatment of severe steroid-refractory acute GvHD with mesenchymal stromal cells
Methods	<p>Type of study: a multicentre, phase III, parallel, double-blind, placebo-controlled randomised trial</p> <p>Countries where study performed: the Netherlands</p>

EUCTR2012-004915-30-NL (Continued)

Intended duration of follow-up: 10 years

Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Grade II-IV acute GvHD with gut and/or liver involvement, confirmed by histology of involved tissues (in case of gut and liver involvement histology of either one of these tissues is considered sufficient); N.B. if the patient is otherwise eligible but histological confirmation at randomisation is lacking, the principal investigator should be contacted.* Non-responsive to consecutive systemic treatment with steroids at a dose of 2 mg/kg and a calcineurin-inhibitor at therapeutic trough levels, defined as: (a) progressive disease or mixed response after 5-6 days of treatment; (b) stage 4 GvHD of gut and/or liver after 5-6 days treatment and: (i) significant deterioration of clinical parameters (gut) or (ii) increase of serum total bilirubin levels in $\mu\text{mol/L}$ (liver) (not attributable to other causes than acute GvHD); (c) progressive disease after initial partial response of maximal 1 grade after 5-7 days of treatment; (d) stable disease after 7 days of treatment Any age Lansky / Karnofsky score of ≥ 20 Signed informed consent by the patient and/or parent(s) or legal guardian(s). <p>Exclusion criteria</p> <ul style="list-style-type: none"> Use of prophylactic MMF or Myfortic ≤ 6 days prior to development of acute GvHD Systemic treatment for acute GvHD other than steroids and a calcineurin inhibitor (budesonide is considered a local treatment) Pre-treatment with steroids ≥ 1 mg/kg for more than 3 days prior to initiation of steroids at a dose of 2 mg/kg for the treatment of acute GvHD Previous treatment with advanced therapy medicinal products (ATMP) potentially interfering with the endpoints of this study; N.B. if the patient has previously been treated with ATMP, the principal investigator should always be contacted prior to registration*. Progressive or relapsing malignant disease in case of NHL, HL, CLL, MM, and $\geq 5\%$ blasts in the bone marrow in case of AML, ALL, CML Requiring ventilator or vasopressor support Poor performance not expected to survive 14 days Known seropositivity of HIV, Hepatitis B and C, HTLV; Known uncontrolled toxicity for DMSO Known anaphylactic reaction to penicillin or streptomycin Known pregnancy Any psychological, familial, sociological and /or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
Interventions	<p>Intervention arm: bone marrow derived ex vivo expanded cryopreserved MSCs ($>1 \times 10^6$)</p> <p>Comparator arm: placebo (unspecified)</p> <p>Prophylactic or therapeutic: therapeutic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Proportion of patients responding to treatment of acute GvHD grade II-IV (with gut and/or liver involvement) at day 29 <p>Secondary outcomes</p> <ul style="list-style-type: none"> Overall survival Progression-free survival Duration of acute GvHD response Time without systemic immunosuppression. Cumulative incidence of non-relapse mortality

EUCTR2012-004915-30-NL (Continued)

- Adverse events
- Incidence of chronic GvHD
- Quality of life
- Immunological monitoring including monitoring of absolute T-cell subsets, B-cells, NK cells as well as biomarkers of acute GvHD

Starting date	November 2013
Contact information	Contact information: Prof. D. W E Fibbe, HOVON Data Center (Phone: +31 107041560; Email: hd-c@erasmusmc.nl)
Notes	<p>Planned enrolment: 150</p> <p>Estimated completion date: November 2023</p> <p>Trial status: ongoing</p>

NCT00972660

Trial name or title	A phase II, randomized study to evaluate the safety and efficacy of ex-vivo cultured allogenic mesenchymal stem cells for the treatment of extensive chronic graft versus host disease
Methods	<p>Type of study: a single-centre, phase II, open-label, parallel, randomised controlled trial</p> <p>Countries where study performed: China</p> <p>Intended duration of follow-up: 2 years</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Informed consent obtained from patient and donor • Any patient who has undergone allogeneic stem cell transplantation with extensive chronic GvHD • Have not received additional agent for cGvHD within 3 months • Expected life is more than 90 days • Adequate pulmonary function with no evidence of chronic obstructive or severe restrictive pulmonary disease • Adequate cardiac function with no evidence of uncontrolled high blood pressure, congestive heart failure, angina pectoris, acute myocardial infarction within 6 months prior to the process <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Invasive fungal disease • Active cytomegalovirus (CMV)/Epstein-Barr virus (EBV)/varicella disease • Patient with a history of hypersensitivity to bovine products • Relapsed malignancy
Interventions	<p>Intervention arm: mesenchymal stem cell (MSC). Patients with newly diagnosed extensive cGvHD: prednisone 1 mg/kg + cyclosporine or tacrolimus and MSC 2×1,000,000 MSC/kg, IV twice a week for the first two weeks and weekly for the following two weeks (6 doses totally). Patients with refractory extensive cGvHD: primary treatment (prednisone + cyclosporine or tacrolimus, or plus mycophenolate mofetil, or plus methotrexate) and MSC 2×1,000,000 MSC/kg, IV twice a week for the first two weeks and weekly for the following two weeks (6 doses totally).</p> <p>Comparator arm: control. Patients with newly diagnosed extensive cGvHD: prednisone 1 mg/kg + cyclosporine or tacrolimus. Patients with refractory extensive cGvHD: primary treatment (e.g. prednisone 1 mg/kg + cyclosporine or tacrolimus, or plus mycophenolate mofetil, or methotrexate).</p>

NCT00972660 (Continued)

Prophylactic or therapeutic: therapeutic

Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Total response rate defined as patients with complete and partial response within first three months <p>Secondary outcomes</p> <ul style="list-style-type: none"> Overall survival Event-free survival Percentage of patients who can taper or discontinue immunosuppressive agents Serum cytokine levels and lymphocyte subsets in patients with chronic GvHD
Starting date	September 2009
Contact information	Principal Investigator: Xing Du, Guangdong General Hospital, Guangzhou, Guangdong, China, 510080
Notes	<p>Planned enrolment: 52</p> <p>Estimated completion date: December 2017</p> <p>Trial status: enrolling patients by invitation only</p>

NCT01045382

Trial name or title	MSC and HSC coinfusion in mismatched minitransplants
Methods	<p>Type of study: a multicentre, phase II, parallel, double-blind, randomised controlled trial</p> <p>Countries where study performed: Belgium</p> <p>Intended duration of follow-up: 2 years</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> Theoretical indication for a standard allo-transplant, but not feasible because: age > 55 years. Unacceptable end organ performance; patient's refusal Indication for a standard auto-transplant: perform mini-allotransplantation 2-6 months after standard autotransplant Male or female; fertile female patients must use a reliable contraception method Age ≤ 75 years old Informed consent given by patient or his/her guardian if of minor age One or two HLA mismatches with PBSC Haematological malignancies confirmed histologically and not rapidly progressing <p>Exclusion criteria</p> <ul style="list-style-type: none"> Any condition not fulfilling inclusion criteria HIV positive Terminal organ failure, except for renal failure (dialysis acceptable) Uncontrolled infection, arrhythmia or hypertension Previous radiation therapy precluding the use of 2 Gy TBI 10/10 HLA-A, -B, -C, DRB1 and DQB1 allele-matched donor fit to/willing to donate PBSC

NCT01045382 (Continued)

Interventions	<p>Intervention arm: patients will receive a conditioning regimen consisting in fludarabine (total dose 90 mg/square meter) and 2 Gy total body irradiation. MSC cells ($1.5\text{--}3.0 \times 10^6$ MSC/Kg BW) will be injected, followed, at least one hour later, by the infusion of HLA-mismatched PBSC from related or unrelated donor</p> <p>Comparator arm: patients will receive a conditioning regimen consisting in fludarabine (total dose 90 mg/² metre) and 2 Gy total body irradiation. Isotonic solution will be injected will be injected, followed, at least one hour later, by the infusion of HLA-mismatched PBSC from related or unrelated donor</p> <p>Prophylactic or therapeutic: prophylactic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Overall survival at 1 year <p>Secondary outcomes</p> <ul style="list-style-type: none"> Incidence of grade II-IV and grade III-IV aGvHD at 100 days Number of absolute donor T cells after HCT in each arm at 28 days Cumulative incidence of non-relapse mortality at 100 days and 1, 2 years Incidence of extensive chronic GvHD in each arm at 1 year Incidence of graft rejection in each arm at 1 year Quality and timing of immunologic reconstitution in each arm at 100 days and 1, 2 years Detection of MSC from donor origin in recipient marrow after HCT in patients given MSC at 40 days Proportion of patients with measurable disease at HCT who achieve a complete response in each arm at 100 days and 1, 2 years Cumulative incidence of relapse at 1 and 2 years Incidence of progression-free survival at 1 and 2 years Incidence of infections at 100 days
Starting date	July 2010
Contact information	<p>Contact information:</p> <p>Yves Beguin (Phone: +32 43667201; Email: yves.beguin@chu.ulg.ac.be)</p> <p>Frédéric Baron (Phone: +32 43667201; Email: F.Baron@ulg.ac.be)</p>
Notes	<p>Planned enrolment: 120</p> <p>Estimated completion date: July 2023</p> <p>Trial status: currently recruiting participants</p>

NCT01589549

Trial name or title	Mesenchymal stromal cells for acute graft versus host disease
Methods	<p>Type of study: a phase 2, parallel, open-label, randomised controlled trial</p> <p>Countries where study performed: Australia</p> <p>Intended duration of follow-up: 1 year</p>
Participants	Inclusion criteria

Mesenchymal stromal cells as treatment or prophylaxis for acute or chronic graft-versus-host disease in haematopoietic stem cell transplant (HSCT) recipients with a haematological condition (Review)

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NCT01589549 (Continued)

- Grades 2-4 acute graft-versus-host disease after bone marrow transplantation up to day +180 after transplantation
- Age 18-55 years
- Must be receiving a calcineurin inhibitor

Exclusion criteria

- Failure to sign informed consent
- Corticosteroid therapy for 72 hours or greater
- ECOG score equal to or greater than 3

Interventions	<p>Intervention arm: corticosteroid therapy (methylprednisolone 2.5 mg/kg intravenously) plus MSCs 2×10^6 intravenously on two occasions at weekly intervals</p> <p>Comparator arm: control: corticosteroid therapy (methylprednisolone 2.5 mg/kg intravenously)</p> <p>Prophylactic or therapeutic: therapeutic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Survival at one year after onset of graft-versus-host disease <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Response at 14 days after commencement of treatment for aGvHD • Response at 28 days after commencement of treatment of aGvHD • Incidence of severe infection at 1 year • Disease-free survival at one year • Time to treatment failure, requiring salvage therapy, at 28 days
Starting date	April 2012
Contact information	<p>Contact information:</p> <p>Duncan Purtill MB, BS (Phone: +61 861523788; Email: duncan.purtill@health.gov.au)</p> <p>Richard Herrmann MB, BS (Phone: +61 892241987; Email richard.herrmann@health.wa.gov.au)</p>
Notes	<p>Planned enrolment: 66</p> <p>Estimated completion date: December 2016</p> <p>Trial status: currently recruiting participants</p>

NCT02241018

Trial name or title	MSCs combined with CD25 monoclonal antibody and calcineurin inhibitors for treatment of steroid-resistant aGvHD
Methods	<p>Type of study: A phase 2/3, parallel, open-label, randomised controlled trial</p> <p>Countries where study performed: China</p> <p>Intended duration of follow-up: 1 year</p>
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Age 14-65 years • Steroid-resistant aGvHD

Mesenchymal stromal cells as treatment or prophylaxis for acute or chronic graft-versus-host disease in haematopoietic stem cell transplant (HSCT) recipients with a haematological condition (Review)

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NCT02241018 (Continued)

- Participants (or their legally acceptable representatives) must have signed an informed consent document

Exclusion criteria

- Any abnormality in a vital sign (e.g. heart rate, respiratory rate, or blood pressure)
- Patients with any conditions not suitable for the trial (investigators' decision)

Interventions

Intervention arm: MSCs given at a median dose of 1×10^6 cells/kg once weekly for 4 dose (as 1 cycle) or until CR. The response should be evaluated at 3 and 4 weeks. If symptoms of aGvHD progress at 3 weeks or the patients have NR at 4 weeks, these patients will switch to other therapy. If patients achieved PR at 4 weeks, another cycle will be given. Besides, CD25 monoclonal antibody (20 mg/kg) will be administered at day 1,4, 8, 15, 21 and calcineurin inhibitors will also be used.

Comparator arm: CD25 monoclonal antibody (20 mg/kg, day 1,4, 8, 15, 21) will be administered combined with calcineurin inhibitors. The response should be evaluated at 3 and 4 weeks. If symptoms of aGvHD progress at 3 weeks or the patients have NR at 4 weeks, these patients will switch to other therapy. If patients achieved PR at 4 weeks, another cycle will be given.

Prophylactic or therapeutic: therapeutic

Outcomes

Primary outcome

- The efficacy of treatment for steroid-resistant aGvHD at 1 year (responses to aGvHD are according to the literature criteria, including completely response (CR), partial response (PR) and no response (NR), and CR is defined as resolution of all symptoms of aGvHD; PR is defined as a decrease by at least 1 GvHD stage in any 1 organ system without deterioration in others 24. Overall response (OR) includes CR and PR).

Secondary outcomes

- Incidence of infections (mainly focused on cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections during study treatments and within one year after study treatments)
- Incidence of primary underlying disease relapse at 1 year
- Incidence of cGvHD at 1 year

Starting date

September 2014

Contact information

Contact information: Ren Lin (Phone: +86 020 62787883; Email: lansinglinren@hotmail.com)

Notes

Planned enrolment: 200

Estimated completion date: December 2018

Trial status: currently recruiting participants

NCT02291770

Trial name or title

Treatment of chronic graft-versus-host disease with mesenchymal stromal cells (MSC-cGvHD)

Methods

Type of study: a multicentre, phase 3, parallel, open-label, randomised controlled trial

Countries where study performed: China

Intended duration of follow-up: 2 years

Participants

Inclusion criteria

- Newly diagnosed cGvHD

NCT02291770 (Continued)

- Informed consent obtained from patient and donor
- Any patient who has undergone allogeneic stem cell transplantation with c GvHD
- Have not received additional agent for cGvHD within 3 months
- Expected life is more than 90 days
- Adequate pulmonary function with no evidence of chronic obstructive or severe restrictive pulmonary disease
- Adequate cardiac function with no evidence of uncontrolled high blood pressure, congestive heart failure, angina pectoris, acute myocardial infarction within 6 months prior to the process

Exclusion criteria

- Invasive fungal disease
- Active cytomegalovirus (CMV)/Epstein-Barr virus (EBV)/varicella disease)
- Patient is with a history of hypersensitivity to bovine products
- Relapsed malignancy

Interventions	<p>Intervention arm: MSC. Primary treatment (prednisone 1 mg/kg + cyclosporine or tacrolimus) and MSC 2×10^6 MSC/kg, intravenously twice a week for the first two weeks and weekly for the following two weeks (6 doses in total)</p> <p>Comparator arm: placebo (not specified) plus primary treatment (prednisone 1 mg/kg + cyclosporine or tacrolimus)</p> <p>Prophylactic or therapeutic: therapeutic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Proportion of patients responding to treatment of cGvHD with MSC at 90 days <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Overall survival at 2 years • Progression-free survival at 2 years • Time without systemic immunosuppression at 2 years • Cumulative incidents of non-relapse mortality at 2 years • Adverse events at 2 years
Starting date	October 2014
Contact information	<p>Contact information:</p> <p>Prof. Xin Du (Phone: +86 02083827812-62122; Email: miyadu@hotmail.com)</p> <p>Prof. Jianyu Weng (Phone: +86 02083827812-62122; Email: wengjianyu1969@163.com)</p>
Notes	<p>Planned enrolment: 130</p> <p>Estimated completion date: December 2019</p> <p>Trial status: currently recruiting participants</p>

NCT02770430

Trial name or title	Mesenchymal stem cells as first treatment line for resistant acute graft versus host disease
Methods	<p>Type of study: A phase 2, cross-over, open-label, randomised controlled trial</p> <p>Countries where study performed: Brazil</p>

Mesenchymal stromal cells as treatment or prophylaxis for acute or chronic graft-versus-host disease in haematopoietic stem cell transplant (HSCT) recipients with a haematological condition (Review)

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NCT02770430 (Continued)

Intended duration of follow-up: 100 days

Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> All patients with refractory and/or resistant steroids GvHD will be included after signing of free and informed consent <p>Exclusion criteria</p> <ul style="list-style-type: none"> Patients who do not agree to participate and do not sign an informed consent and patients who are Grade I refractory GvHD
Interventions	<p>Intervention arm: MSCs derived from BM will be isolated and expanded in the laboratory under conditions of Good Manufacturing Practice. The quality control involves immunophenotyping, differentiation, microbiological control, mycoplasma and endotoxin tests. Patients will receive five infusions of MSC. Dosage: 2×10^6 cells/kg</p> <p>Comparator arm: control (basiliximab 20 mg dose for adults and 10 mg for children, 1 time per week or every 3 days if the stage of GvHD worsens until reaching Very Good Partial Response (VG-PR) or for a maximum of 4 doses, whichever comes first. If after this a VGPR is not found: Infliximab 5 mg to 10 mg/kg dose, 1 time a week, four weeks or even VGPR.</p> <p>Prophylactic or therapeutic: therapeutic</p>
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> Complete response: disappearance of all symptoms at day 28 <p>Secondary outcomes</p> <ul style="list-style-type: none"> Partial response: with a decrease at least of one degree of GvHD at day 28 Decrease to the stage I of GvHD at day 28 Stable disease: when there is a stability of the disease (by clinical evaluation) at day 28 Number of infection (by clinical and laboratory evaluation) at day 100 Type of infection (by clinical and laboratory evaluation) at day 100
Starting date	September 2015
Contact information	<p>Contact information:</p> <p>Lucia Silla, PhD (Principal investigator) (Phone +55 51 33597516; Email: dralucia.silla@gmail.com)</p> <p>Vanessa Valim, MSc (Phone +55 51 33598850; Email: vanessavalim@gmail.com)</p>
Notes	<p>Planned enrolment: 90</p> <p>Estimated completion date: December 2018</p> <p>Trial status: currently recruiting participants</p>

aGvHD: acute graft-versus-host disease; **cGvHD:** chronic graft-versus-host disease; **ALL:** acute lymphoblastic leukaemia; **AML:** acute myeloid leukaemia; **ATG:** antithymocyte globulin; **CML:** chronic myeloid leukaemia; **BM:** bone marrow; **CMV:** cytomegalovirus; **CR:** complete remission; **DLCO:** diffusion capacity of the lung for carbon monoxide; **DLI:** donor lymphocyte infusion; **DMSO:** Dimethyl sulphoxide; **ECOG:** Eastern Cooperative Oncology Group; **FEV:** forced expiratory volume; **HLA:** human leukocyte antigen; **HSCT:** haematopoietic stem cell transplant; **KPS:** Karnofsky Performance Status; **MDS:** myelodysplastic syndrome; **MSC:** mesenchymal stromal cells; **NHL:** non-Hodgkins lymphoma; **NK cells:** natural killer cells; **PBSC:** peripheral blood stem cells; **PR:** partial remission; **RAEB:** refractory anaemia with excess myeloblasts; **TBI:** total body irradiation;

DATA AND ANALYSES

Comparison 1. MSCs vs. control/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	6		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 Prophylactic trials	5		Hazard Ratio (Random, 95% CI)	0.85 [0.50, 1.42]
1.2 Therapeutic trials	1		Hazard Ratio (Random, 95% CI)	1.12 [0.80, 1.56]
2 Relapse of malignant disease	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Short-term follow-up ($\leq$ 12 months)	2	275	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.37, 1.84]
2.2 Long-term follow-up ($>$ 12 months)	6	323	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.73, 1.59]
3 Infections	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 CMV	3	100	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.71, 1.50]
4 Incidence of aGvHD (prophylactic trials)	6	247	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.63, 1.17]
5 Incidence of cGvHD (prophylactic trials)	6	283	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.49, 0.89]
6 Acute GvHD complete response (therapeutic trials)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Acute GvHD partial response (therapeutic trials)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Chronic GvHD complete response (therapeutic trials)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Chronic GvHD partial response (therapeutic trials)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 MSCs vs. control/placebo, Outcome 1 All-cause mortality.

Analysis 1.2. Comparison 1 MSCs vs. control/placebo, Outcome 2 Relapse of malignant disease.

Analysis 1.3. Comparison 1 MSCs vs. control/placebo, Outcome 3 Infections.

Analysis 1.4. Comparison 1 MSCs vs. control/placebo, Outcome 4 Incidence of aGvHD (prophylactic trials).

Analysis 1.5. Comparison 1 MSCs vs. control/placebo, Outcome 5 Incidence of cGvHD (prophylactic trials).

Analysis 1.6. Comparison 1 MSCs vs. control/placebo, Outcome 6 Acute GvHD complete response (therapeutic trials).

Study or subgroup	MSCs n/N	No MSCs n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Osiris Protocol 280	60/173	26/87		1.16[0.79,1.7]
Favours no MSCs				Favours MSCs

Analysis 1.7. Comparison 1 MSCs vs. control/placebo, Outcome 7 Acute GvHD partial response (therapeutic trials).

Study or subgroup	MSCs n/N	No MSCs n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Osiris Protocol 280	2/14	1/14		2[0.2,19.62]
Favours no MSCs				Favours MSCs

Analysis 1.8. Comparison 1 MSCs vs. control/placebo, Outcome 8 Chronic GvHD complete response (therapeutic trials).

Study or subgroup	MSCs n/N	No MSCs n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Zheng 2015	15/30	1/10		5[0.75,33.21]
Favours no MSCs				Favours MSCs

Analysis 1.9. Comparison 1 MSCs vs. control/placebo, Outcome 9 Chronic GvHD partial response (therapeutic trials).

Study or subgroup	MSCs n/N	No MSCs n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Zheng 2015	12/30	2/10		2[0.54,7.45]
Favours no MSCs				Favours MSCs

Comparison 2. MSCs high dose vs. low dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (all trials)	1		Hazard Ratio (Random, 95% CI)	0.0 [0.0, 0.0]
2 Acute GvHD complete response (therapeutic trials)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Acute GvHD partial response (therapeutic trials)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Chronic GvHD complete response (therapeutic trials)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 MSCs high dose vs. low dose, Outcome 1 All-cause mortality (all trials).

Study or subgroup	MSCs N	No MSCs N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Jurado 2017	0	0	0 (0)			Not estimable
Total (95% CI)						Not estimable
Heterogeneity: Not applicable Test for overall effect: Not applicable

Analysis 2.2. Comparison 2 MSCs high dose vs. low dose, Outcome 2 Acute GvHD complete response (therapeutic trials).

Study or subgroup	High dose MSCs n/N	Low dose MSCs n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Osiris Protocol 260	10/15	14/16		0.76[0.51,1.14]
Favours low dose MSCs				
Favours high dose MSCs				

Analysis 2.3. Comparison 2 MSCs high dose vs. low dose, Outcome 3 Acute GvHD partial response (therapeutic trials).

Study or subgroup	High dose MSCs n/N	Low dose MSCs n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Osiris Protocol 260	5/15	0/16		11.69[0.7,194.79]
Favours low dose MSCs				
Favours high dose MSCs				

Analysis 2.4. Comparison 2 MSCs high dose vs. low dose, Outcome 4 Chronic GvHD complete response (therapeutic trials).

Study or subgroup	High dose MSCs n/N	Low dose MSCs n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jurado 2017	5/9	3/5		0.93[0.37,2.33]
Favours low dose MSCs				
Favours high dose MSCs				

Comparison 3. MSCs vs. control/placebo: malignant versus non-malignant disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of aGvHD (prophylactic trials)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Malignant disease	5	199	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.60, 1.14]
1.2 Non-malignant disease	1	48	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.45, 4.28]

Analysis 3.1. Comparison 3 MSCs vs. control/placebo: malignant versus non-malignant disease, Outcome 1 Incidence of aGvHD (prophylactic trials).

ADDITIONAL TABLES

Table 1. Characteristics of participants

Study	Patient population	HSCT source	Conditioning regimen	GvHD prophylaxis	Treatment arm	Number randomised	Number analysed	Age distribution (years)	% Female	Disease	Stage	GvHD involvement
Gao 2016	HLA-haploidentical transplants, haematological malignancies without ongoing or cGvHD	n/r	ALL: TBI plus Ara-C, CY and ATG. AML/MDS: CC-NU, Ara-C, BU, CY and ATG.	CSA, MMF, and short term MTX.	MSCs	62	62 (ITT)	< 18 (15), 18-40 (39), > 40 (8)	53.2%	AML (43), ALL (14), MDS (5)	CR1 (48), CR2 (8), PR (6)	N/A
					Placebo	62	62 (ITT)	< 18 (13), 18-40 (43), > 40 (6)	51.6%	AML (42), ALL (16), MDS (4)	CR1 (39), CR2 (15), PR (8)	N/A
Ghavamzadeh 2010	Thalas-saemia major	PB or BM	CY or fludarabine based	CSA, MTX	MSCs	25	25	median 17	32.0%	N/A	Class III	N/A
					Control	23	23	median 16	48.0%	N/A	Class III	N/A
Jurado 2017	Haematological malignancies; cGvHD	PB	MAC (3), RIC (11)	CSA, prednisone	MSCs (3 x 10 ⁶ cells/kg)	6	5	mean 45.5 (SD 7.92)	33.3%	lymphomas (3), acute leukemias (2), myeloma (0)	n/r	cGvHD: moderate (3), severe (2)
					MSCs (1 x 10 ⁶ cells/kg)	9	9	mean 51.1 (SD 10.85)	80.0%	lymphomas (6), acute leukemias (2), myeloma (1)	n/r	cGvHD: moderate (4), severe (5)
Kuzmina 2012	Haematological malignancies; aGvHD	n/r	MAC (27), RIC (10)	CSA, MTX, some additionally received MMF or prednisolone.	MSCs	19	19	median 34 (range 20-63)	57.8%	AML/MDS (14), ALL (2), CML (3), CLL (0)	CR (19), non-CR (0)	N/A
					Control	18	18	median 29 (range 19-60)	61.0%	AML/MDS (10), ALL (4), CML (3), CLL (1)	CR (15), non-CR (3)	N/A
Liu 2011	Haematological malignancies	G-CSF mobilised	BU, CA, CY, ATG	CSA, MTX	MSCs	30	27	median 30 (range 14-46)	32.0%	ALL (8), AML (13), CML (6), High risk (6)	CR1 (23), CR2 (4)	N/A

Table 1. Characteristics of participants (Continued)

	in complete remission	BM and PB				Control	30	28	medi-an 31.5 (range 12-48)	26.0%	ALL (16), AML (7), CML (5), High risk (6)	CR1 (24), CR2 (4)	N/A
Mareika 2016	Haemato-logical ma-lignancies	n/r	n/r	n/r	MSCs	n/r	10	median 13 (range 5-24) (all partici-pants)	n/r	ALL (8), AML (2)	n/r	N/A	
					Control	n/r	12	median 13 (range 5-24) (all partici-pants)	n/r	ALL (7), AML (4), MDS (1)	n/r	N/A	
Ning 2008	Haemato-logical ma-lignancies	PB (16), BM (10), PB+BM (4)	TBI, CY (BU, CY in one patient)	CSA, MTX	MSCs	15	10	median 38 (range 17-52)	26.6%	AML (8), CML (4), ALL (2), MDS (1)	CR1 (9), CP (3), first re-lapse (1), CP2 (1), RAS (1)	N/A	
					Con-trol (no placebo)	15	15	median 37 (range 16-61)	13.3%	AML (7), CML (4), ALL (2), NHL (1), MDS (1)	CR1 (8), CR2 (1), CP (2), CP2 (2), RAS (1), non-re-lapse (1)	N/A	
Osiris Protocol 260	Haemato-logical ma-lignancies; acute GvHD II-IV requir-ing systemic steroid ther-apy	PB (30), BM (1)	MAC (15), RIC (8), non-mye-loabla-tive(4), DLI (4)	CsA (6), tacrolimus (10), tacrolimus plus MMF or MTX (11)	MSCs (8 x 10 ⁶ cells/kg)	16	15	median 49 (range 34-67)	33.3%	AML/MDS (8), NHL (2), CLL (1), ALL (3), MM (1)	n/r	aGvHD: grade II (10), grade III (4), grade IV (1)	
					MSCs (2 x 10 ⁶ cells/kg)	16	16	median 53 (range 42-67)	31.3%	AML/MDS (6), NHL (3), CLL (3), ALL (1), MMF (2), MM (0), Hodgkin's (1)	n/r	aGvHD: grade II (11), grade III (3), grade IV (2)	

Table 1. Characteristics of participants (Continued)

Osiris Protocol 265	Haemato-logical malignancies; newly diagnosed aGvHD grades B-D	BM/PB/CB/DLI	n/r	MTP (or equivalent)	MSCs	n/r [192 in total]	n/r [192 in total]	n/r	n/r	n/r	n/r	aGvHD: grade B-D, mostly skin
					Placebo	n/r	n/r	n/r	n/r	n/r	n/r	aGvHD: grade B-D, mostly skin
Osiris Protocol 280	Haemato-logical malignancies; steroid-refractory aGvHD	PB (197), other (63)	MAC (177), other (83)	"Standard of care"	MSCs	173	173 (ITT)	mean 42.3 (SD 17.2) (all participants)	n/r	AML (49), other (124)	n/r	aGvHD: grade B (38), grade C (88), grade D (47).
					Placebo	87	87 (ITT)	mean 42.3 (SD 17.2) (all participants)	n/r	AML (23), other (64)	n/r	aGvHD: grade B (23), grade C (50), grade D (14)
Wu 2013	Haemato-logical malignancies (high risk leukaemia)	CB	ALL: CY, etoposide, TBI AML: BU, CY	CSA, MTP, ATG	MSCs	8	8	median 9.8 (range 3.2-12.1)	37.5%	ALL (3), AML (5)	2nd remission (3), MDS (2), Ph (2), monosomy 7 (1)	aGvHD: none (4), grade I (3), grade II (1). cGvHD: none (7), limited (1)
					Control	12	12	median 8.5 (range 3.6-13.1)	50.0%	ALL (5), AML (7)	2nd remission (6), 1st remission (2), MDS (2), Ph (2)	aGvHD: none (4), grade I (5), grade II (2), grade III (1) cGvHD: none (7), limited (4), extensive (1)
Zheng 2015	Haemato-logical malignancies, extensive cGvHD	n/r	n/r	n/r	MSCs	30	30	n/r	n/r	n/r	n/r	extensive cGvHD in skin and/or liver
					Control	10	10	n/r	n/r	n/r	n/r	extensive cGvHD in skin and/or liver

aGvHD: acute graft-versus-host disease; **ALL:** acute lymphoblastic leukaemia; **AML:** acute myeloid leukaemia; **Ara-C:** arabinosylcytosine; **ATG:** antithymocyte globulin; **BU:** busulphan; **CA:** cytosine arabinoside; **CB:** cord blood; **CCNU:** chlorethyl cyclohexyl nitrosourea; **cGvHD:** chronic graft-versus-host disease; **CLL:** chronic lymphoid leukaemia; **CML:** chronic myeloid leukaemia; **CP:** chronic phase; **CP2:** second chronic phase; **CR:** complete remission; **CR1:** complete first remission; **CR2:** complete second remission; **CSA:** cyclosporine A; **CY:** cyclophosphamide; **DLI:** donor lymphocyte infusion; **ITT:** intention-to-treat; **MAC:** myeloablative conditioning; **MDS:** myelodysplastic syndrome; **MF:** myelofibrosis; **MM:** multiple myeloma; **MMF:** mycophenolate mofetil; **MSC:** mesenchymal stromal cells; **MTP:** methylprednisolone; **MTX:** methotrexate; **N/A:** not applicable; **NHL:** non-Hodgkins lymphoma; **PB:** peripheral blood; **Ph:** Philadelphia chromosome; **PR:** partial remission; **RAS:** refractory anaemia with ringed sideroblasts; **RIC:** reduced intensity conditioning; **TBI:** total body irradiation;

Table 2. Characteristics of interventions

Study	Prophylactic or therapeutic	Source of MSCs	Expansion protocol	Dose/Schedule	Timing	Comparator
Gao 2016	Prophylactic	UC	n/r	3 x 10 ⁷ cells/100mL	Post-transplantation (+4,+5,+6 and +7 months)	Placebo (100 mL normal saline at +4,+5,+6 and +7 months)
Ghavamzadeh 2010	Prophylactic	n/r	n/r	1.45-1.8 x 10 ⁶ cells/kg given in single intravenous infusion	Co-transplantation (4 hours prior to HSCT)	Control (no placebo)
Jurado 2017	Therapeutic	AT	Fetal bovine serum	3 x 10 ⁶ cells/kg given as a single infusion	Post-transplantation (within first week of cGvHD therapy)	1 x 10 ⁶ cells/kg given as a single infusion
Kuzmina 2012	Prophylactic	BM	Platelet lysate	~10 ⁶ (range 0.9 - 1.39) cells/kg as single infusion	Co-transplantation (Injected at the time of graft activation (leukocytes >1 x 10 ⁹ /L))	Control (no placebo)
Liu 2011	Prophylactic	BM	Nutrient mixture of F12, 42% MCDB-201 medium and 58% DMEM	3-5 x 10 ⁵ cells/kg	Co-transplantation (within 24 hours of HSCT)	Control (no placebo)
Mareika 2016	Prophylactic	BM	n/r	1.56 +/- 0.4 x 10 ⁶ cells/kg	Co-transplantation (timing n/r)	Control (no placebo)
Ning 2008	Prophylactic	BM	Fetal bovine serum	Median 3.3 (range 0.3-15.3) x 10 ⁵ cells/kg given intravenously over 30 minutes	Co-transplantation (4 hours prior to HSCT)	Control (no placebo)
Osiris Protocol 260	Therapeutic	BM	Fetal bovine serum	8 x 10 ⁶ cells/kg in two infusions given intravenously 3 days apart.	Post-transplantation (first infusion within 24-48 hours of aGvHD diagnosis)	2 x 10 ⁶ cells/kg in two infusions given intravenously 3 days apart.
Osiris Protocol 265	Therapeutic	BM	Fetal bovine serum	2 x 10 ⁶ cells/kg, total 6 infusions over 4 weeks: twice weekly for 2 weeks, then weekly for 2 weeks	Post-transplantation (first infusion within 72 hours of aGvHD diagnosis)	Placebo (excipient, less cells, total 6 infusions over 4 weeks: twice weekly for 2 weeks, then weekly for 2 weeks)
Osiris Protocol 280	Therapeutic	BM	n/r	2 x 10 ⁶ cells/kg, given as 8 infusions over 4 weeks, at least 3 days apart	Post-transplantation (timing n/r)	Placebo (iv infusions equivalent to the calculated volume of active treatment)

Table 2. Characteristics of interventions (Continued)

Wu 2013	Prophylactic	UC	Fetal bovine serum	Median 7.19 (range 2.44 to 10.12) x 10 ⁶ cells/kg infused over 30 minutes through central venous line	Co-transplantation (4 hours prior to HSCT)	Control (no placebo)
Zheng 2015	Therapeutic	n/r	n/r	1-4 x 10 ⁷ cells/week, given weekly over four weeks, total 4.8-16 x 10 ⁷	Post-transplantation (timing n/r)	Control (no placebo)

AT: adipose tissue; **B:M** bone marrow; **DMEM:** Dulbecco's Modified Eagle's medium; **UC:** umbilical cord; n/r not reported; **PL:** platelet lysate; **BF:** fetal bovine serum

Table 3. Engraftment of platelets and neutrophils

Study	MSC dose/schedule	Definition of platelet engraftment	Time to platelet engraftment		Definition of neutrophil engraftment	Time to neutrophil engraftment	
			MSCs	No MSCs		MSCs	No MSCs
Ghavamzadeh 2010	1.45-1.8 x 10 ⁶ cells/kg given in single intravenous infusion	> 20 x 10 ⁹ /L	Median 16 days (range n/r)	Median 15 days (range n/r)	> 0.5 x 10 ⁹ /L	Median 14 days (range n/r)	Median 13 days (range n/r)
Liu 2011	3-5 x 10 ⁵ cells/kg	>20 x 10 ⁹ /L for 7 consecutive days	Median 19.5 (range 8-52) days	Median 20 (range 10-80) days	> 0.5 x 10 ⁹ /L for 3 consecutive days	Median 12 (range 10-21) days	Median 12 (range 10-23) days
Mareika 2016	1.56 +/- 0.4 x 10 ⁶ cells/kg	n/r	Median 18 (range 10-44) days	Median 23 (range 16-144) days	n/r	Median 19 (range 12-20) days	Median 24 (range 16-45) days
Ning 2008	Median 3.3 (range 0.3-15.3) x 10 ⁵ cells/kg given intravenously over 30 minutes	> 50 x 10 ⁹ /L (first of 3 consecutive days)	Median 30 (range 16-45) days	Median 27 (15-64) days	> 0.5 x 10 ⁹ /L (first of 3 consecutive days)	Median 16 (range 12-21) days	Median 15 (range 11-20) days
Wu 2013	Median 7.19 (range 2.44 to 10.12) x 10 ⁶ cells/kg infused over 30 minutes	> 20 x 10 ⁹ /L	Median 30 (range 20-45) days	Median 73 (42-135) days	> 0.5 x 10 ⁹ /L	Median 12 (range 8-16) days	Median 21 (range 17-43) days

n/r not reported

APPENDICES

Appendix 1. The Cochrane Library search strategy

- #1 MeSH descriptor: [Mesenchymal Stem Cell Transplantation] this term only
- #2 MeSH descriptor: [Mesenchymal Stromal Cells] this term only
- #3 mesenchymal* or mesenchimal* or multistem or remestemcel* or Prochymal or MSCs
- #4 ((marrow or multipotent) near/4 stromal) or (wharton* next jelly)
- #5 #1 or #2 or #3 or #4

Appendix 2. MEDLINE (OvidSP) search strategy

1. Mesenchymal Stem Cell Transplantation/
2. Mesenchymal Stromal Cells/
3. (mesenchymal* or mesenchimal* or multistem or remestemcel* or Prochymal).tw,kf.
4. (((marrow or multipotent) adj4 stromal) or (wharton* adj jelly)).tw,kf.
5. 1 or 2 or 3 or 4
6. exp Hematopoietic Stem Cells/
7. Hematopoietic Stem Cell Transplantation/
8. Cord Blood Stem Cell Transplantation/
9. Peripheral Blood Stem Cell Transplantation/
10. ((cord blood or cord stem or marrow stem or placental blood or peripheral blood) adj5 transplant*).tw,kf.
11. (haematopo?etic or hematopo?etic or haemopo?etic or hemopo?etic or haematocytopo?etic or hematocytopo?etic or HSCT).tw,kf.
12. (cotransplant* or coinfus* or co-transplant* or co-infus* or HLA-matched or HLA-identical or haploidentical).tw,kf.
13. Graft vs Host Disease/
14. (graft-vs-host or graft vs host or graftvshost or graftvs host or graft vshost or graftversushost or graft versus host or graft-versus-host or graftversus host or graft versushost or GvHD or GVH disease or GVH reaction*).tw,kf.
15. or/6-14
16. 5 and 15
17. Meta-Analysis.pt.
18. ((meta analy* or metaanaly*) and (trials or studies)).ab.
19. (meta analy* or metaanaly* or evidence-based).ti.
20. ((systematic* or evidence-based) adj3 (review* or overview*)).tw,kf.
21. (cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or citation index or psyclit or psychlit or psycinfo or psychinfo or "web of science" or scopus).ab.
22. Cochrane Database of systematic reviews.jn.
23. ((literature or systematic* or comprehensive* or electronic*) adj2 search*).ab.
24. (additional adj (papers or articles or sources)).ab.
25. (bibliograph* or handsearch* or hand search* or manual* search* or searched or reference list*).ab.
26. (relevant adj (journals or articles)).ab.
27. or/17-26
28. Review.pt.
29. RANDOMIZED CONTROLLED TRIALS AS TOPIC/
30. selection criteria.ab. or critical appraisal.ti.
31. (data adj (extraction or analys*)).ab.
32. RANDOMIZED CONTROLLED TRIALS/
33. or/29-32
34. 28 and 33
35. 27 or 34
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. randomi*.tw,kf.
39. placebo.ab.
40. clinical trials as topic.sh.
41. randomly.ab.
42. groups.ab.
43. trial.tw.
44. or/36-43
45. 35 or 44
46. (ANIMALS/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/) not HUMANS/
47. (Comment or Editorial).pt.
48. 46 or 47

49. 45 not 48
50. 16 and 49

Appendix 3. Embase (OvidSP) search strategy

1. mesenchymal stem cell/ or mesenchymal stroma cell/
2. mesenchymal stem cell transplantation/
3. (mesenchymal* or mesenchimal* or multistem or remestemcel* or Prochymal or MSCs).tw,kw.
4. (((marrow or multipotent) adj4 stromal) or (wharton* adj jelly)).tw,kw.
5. 1 or 2 or 3 or 4
6. hematopoietic stem cell/
7. exp hematopoietic stem cell transplantation/
8. cord blood stem cell transplantation/
9. exp peripheral blood stem cell transplantation/
10. ((cord blood or cord stem or placental blood or peripheral blood) adj5 transplant*).tw,kw.
11. (haematopo?etic or hematopo?etic or haemopo?etic or hemopo?etic or haematocytopo?etic or hematocytopo?etic or HSCT).tw,kw.
12. (cotransplant* or coinfus* or co-transplant* or co-infus* or HLA-matched or HLA-identical or haploidentical).tw,kw.
13. exp graft versus host reaction/
14. (graft-vs-host or graft vs host or graftvshost or graftvs host or graft vshost or graftversushost or graft versus host or graft-versus-host or graftversus host or graft versushost or GvHD or GVH disease or GVH reaction*).tw,kw.
15. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 5 and 15
17. Meta Analysis/
18. Systematic Review/
19. (meta analy\$ or metaanalys\$).tw.
20. (systematic adj2 (review\$ or overview\$ or search\$)).tw.
21. (literature adj2 (review\$ or overview\$ or search\$)).ti,ab.
22. (cochrane or embase or cinahl or cinhal or lilacs or BIDS or science citation index or psyclit or psychlit or psycinfo or psychinfo or cancerlit).ti,ab.
23. (electronic\$ adj (sources or resources or databases)).ab.
24. reference lists.ab.
25. (bibliograph\$ or handsearch\$ or hand search\$ or manual\$ search\$).ab.
26. (hand-search\$ or handsearch\$).ab.
27. (additional adj (papers or articles or sources)).ab.
28. (relevant adj (journals or articles)).ab.
29. (search term\$ or published articles or search strateg\$).ab.
30. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. data extraction.ab.
32. selection criteria.ab.
33. 31 or 32
34. review.pt.
35. 33 and 34
36. editorial.pt.
37. 30 or 35
38. 37 not 36
39. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
40. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocat* or volunteer*).mp.
41. 39 or 40
42. 38 or 41
43. 16 and 42
44. limit 43 to embase

Appendix 4. CINAHL (NHS Evidence) search strategy

- S1 TX (mesenchymal* or mesenchimal* or multistem or remestemcel* or Prochymal or MSCs)
S2 TX (((marrow or multipotent) N4 stromal) or (wharton* jelly))
S3 S1 OR S2
S4 (MH "Hematopoietic Stem Cells")
S5 (MH "Hematopoietic Stem Cell Transplantation")
S6 TX ((cord blood or cord stem or marrow stem or placental blood or peripheral blood) N5 transplant*)
S7 TX (marrow stem or haematopo?etic or hematopo?etic or haemopo?etic or hemopo?etic or haematocytopo?etic or hematocytopo?etic or HSCT)

S8 TX (cotransplant* or coinfus* or co-transplant* or co-infus* or HLA-matched or HLA-identical or haploidentical)
 S9 (MH "Graft Versus Host Disease")
 S10 TX (graft-vs-host or graft vs host or graftvshost or graftvs host or graft vshost or graftversushost or graft versus host or graft-versus-host or graftversus host or graft versushost or GvHD or GVH disease or GVH reaction*)
 S11 S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10
 S12 S3 AND S11
 S13 (MH Clinical Trials+)
 S14 PT Clinical Trial
 S15 TI ((controlled trial*) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))
 S16 TI ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*)) OR AB ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*))
 S17 TI randomi* OR AB randomi*
 S18 MH RANDOM ASSIGNMENT
 S19 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))
 S20 (TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*))))
 S21 MH PLACEBOS
 S22 MH META ANALYSIS
 S23 MH SYSTEMATIC REVIEW
 S24 TI ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*") OR AB ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*")
 S25 TI ("literature review" OR "literature overview" OR "literature search*") OR AB ("literature review" OR "literature overview" OR "literature search*")
 S26 TI (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit) OR AB (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit)
 S27 TI placebo* OR AB placebo*
 S28 MH QUANTITATIVE STUDIES
 S29 S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28
 S30 S12 AND S29

Appendix 5. PubMed search strategy

#1 (mesenchymal* OR mesenchimal* or multistem or remestemcel* or Prochymal or MSCs)
 #2 (((marrow or multipotent) AND stromal) OR wharton* jelly)
 #3 #1 OR #2
 #4 ((cord blood or cord stem or marrow stem or placental blood or peripheral blood) AND transplant*)
 #5 (haematopoietic or hematopoietic or haemopoetic or hemopoetic or haematocytopenic or hematocytopenic or haematopoietic or hematopoietic or haemopoietic or hemopoietic or haematocytopenic or hematocytopenic OR HSCT OR cotransplant* or coinfus* or co-transplant* or co-infus* or HLA-matched or HLA-identical or haploidentical)
 #6 (graft-vs-host or graft vs host or graftvshost or graftvs host or graft vshost or graftversushost or graft versus host or graft-versus-host or graftversus host or graft versushost or GvHD or GVH disease or GVH reaction*)
 #7 #4 OR #5 OR #6
 #8 #3 and #7
 #9 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR pubmed OR cochrane OR embase) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
 #10 #8 AND #9

Appendix 6. LILACS search strategy

(tw:(mesenchymal OR mesenchymal OR multistem OR remestemcel-l OR prochymal) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:(("clinical_trials")) AND (instance:"regional"))

Appendix 7. Web of Science CPCI-S search strategy

#1 TS=(mesenchymal* OR mesenchimal* or multistem or remestemcel* or Prochymal OR MSCs)
 #2 TS=((marrow or multipotent) AND stromal) OR wharton* jelly
 #3 #1 OR #2
 #4 TS=((cord blood or cord stem or marrow stem or placental blood or peripheral blood) AND transplant*)
 #5 TS=(haematopoietic or hematopoietic or haemopoetic or hemopoetic or haematocytopenic or hematocytopenic or haematopoietic or hematopoietic or haemopoietic or hemopoietic or haematocytopenic or hematocytopenic OR HSCT OR cotransplant* or coinfus* or co-transplant* or co-infus* or HLA-matched or HLA-identical or haploidentical)
 #6 TS=(graft-vs-host or graft vs host or graftvshost or graftvs host or graft vshost or graftversushost or graft versus host or graft-versus-host or graftversus host or graft versushost or GvHD or GVH disease or GVH reaction*)

#7 #4 OR #5 OR #6

#8 #3 and #7

#9 TS=(random* OR "controlled trial" OR "control group" OR "controlled study" OR "systematic review" OR blind*) OR TI=(randomi* OR trial OR systematic)

#10 #8 AND #9

Appendix 8. ClinicalTrials.gov search strategy

Interventional Studies | (MSCs OR mesenchymal OR multistem OR remestemcel OR prochymal OR MSCs) AND (cord blood OR hematopoietic or hemopoietic or hematocytopoietic OR HSC OR HSCT OR co-transplantation or co-infusion or haploidentical OR GVHD) AND (randomized OR random)

Appendix 9. WHO ICTRP search strategy

Intervention: (mesenchymal OR MSCs OR multistem OR remestemcel OR prochymal) AND

Title: (randomized OR randomised OR randomly OR random)

OR

randomized AND mesenchymal AND hematopoietic

OR

randomised AND mesenchymal AND haematopoietic

OR

randomly AND mesenchymal AND hematopoietic

Appendix 10. HKUCTR search strategy

mesenchymal OR MSCs OR multistem OR remestemcel OR prochymal

Appendix 11. Therapeutic Goods Administration copyright notice

We retain the following copyright notice associated with the "Australian Public Assessment Report for Remestemcel-L, ex vivo adult human mesenchymal stem cells, 2015" and "Extract from the clinical evaluation report for Remestemcel-L, ex vivo adult human mesenchymal stem cells, 2015", Therapeutic Goods Administration, used by permission of the Australian Government [<https://www.tga.gov.au/node/537352>]:

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CONTRIBUTIONS OF AUTHORS

Sheila Fisher: screening and selection of trials, data extraction, 'Risk of bias' assessment, data analysis, methodological and content expert.

Antony Cutler: development of the protocol, screening and selection of trials, data extraction, 'Risk of bias' assessment, content expert.

Carolyn Dorée: development of the protocol, development and implementation of search strategies, Information Specialist.

Susan Brunskill: development of the protocol, development of the data extraction form, methodological expert.

Simon Stanworth: development of the protocol, content expert.

Cristina Navarrete: development of the protocol, content expert.

John Girdlestone: development of the protocol, screening and selection of trials, data extraction, Risk' of bias assessment, content expert.

DECLARATIONS OF INTEREST

Sheila Fisher: none known.

Antony Cutler: has received funding for basic and translational research from the Leukemia and Lymphoma Research charity and the NIHR.

Carolyn Dorée: none known.

Susan Brunskill: none known.

Simon Stanworth: none known.

Cristina Navarrete: none known.

John Girdlestone: none known.

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Internal sources

- Research & Development, NHS Blood and Transplant, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The scope of this review has changed since the original protocol was published. Firstly, during early literature searches it became clear that the majority of trials administered MSCs as prophylaxis for GvHD rather than treatment. We therefore extended the scope of the review to include trials which administered MSCs as prophylaxis for GvHD as well as those in which MSCs were given therapeutically. We revised our secondary outcomes to include those relevant to all trials (survival, health-related quality of life, relapse of malignant disease, infection rates and engraftment), outcomes specific to prophylactic trials (incidence of acute and chronic GvHD) and outcomes specific to therapeutic trials (complete and partial response to acute and chronic GvHD). Secondly, in light of the above, we considered that inclusion of trials in which MSCs were given in patients with autoimmune disease or those who had undergone solid organ transplant led to the scope of the review being too diverse, and therefore have removed these participant groups from the review.

We now use random-effects models throughout the review due to expected clinical heterogeneity due to differences in participant characteristics, cell doses and follow-up time points.

A number of databases were removed from the search strategy for the updated review for the following reasons:

- Transfusion Evidence Library - database no longer includes stem cell studies;
- ISRCTN register, EU Clinical Trials Register & UMIN-CTR Japanese Clinical Trials Registry - databases now included within WHO ICTRP;
- KoreaMed, IndMed & PakMediNet - databases now removed from all searches performed by the Systematic Review Initiative for having produced no unique records during an extended search test period.

We had intended to handsearch conference proceedings (Haematopoietic Stem Cell Transplantation for Severe Autoimmune Diseases 2009 (in Bone Marrow Transplantation) and American Society of Blood and Marrow Transplantation/BMT Tandem Meetings 2000 to 2009 (supplements in Biology of Blood and Marrow Transplantation)) but were unable to do this due to a lack of resources.

INDEX TERMS

Medical Subject Headings (MeSH)

*Mesenchymal Stem Cell Transplantation [mortality]; Acute Disease; Chronic Disease; Graft vs Host Disease [epidemiology] [*therapy]; Hematologic Neoplasms [mortality] [*therapy]; Hematopoietic Stem Cell Transplantation [*adverse effects]; Incidence; Randomized Controlled Trials as Topic; Recurrence; beta-Thalassemia [*therapy]

MeSH check words

Humans