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[Intervention Review]

Extracorporeal photopheresis versus alternative treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients

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ABSTRACT

Background

Chronic graft-versus-host disease (GvHD) is a major cause of morbidity and mortality after haematopoietic stem cell transplantation occurring in 6% to 65% of the recipients. Currently, the therapeutic mainstay for chronic GvHD are corticosteroids that are frequently combined with other immunosuppressive agents in people with steroid-refractory manifestations. There is no established standard treatment for steroid-refractory chronic GvHD. The therapeutic options for these patients include extracorporeal photopheresis (ECP), an immunomodulatory treatment that involves ex vivo collection of mononuclear cells from peripheral blood, exposure to the photoactive agent 8-methoxypsoralen, ultraviolet radiation and re-infusion of the processed cell product. The mechanisms of action of ECP are not completely understood. This is an updated version of a Cochrane review first published in 2014.

Objectives

To evaluate the effectiveness and safety of ECP for the management of chronic GvHD in children and adolescents after haematopoietic stem cell transplantation.

Search methods

We searched the Cochrane Register of Controlled Trials (CENTRAL) (Issue 9, 2015), MEDLINE and EMBASE databases from their inception to 23 September 2015. We searched the reference lists of potentially relevant studies without any language restriction. We searched eight trial registers and five conference proceedings on 29 September 2015.

Selection criteria

Randomised controlled trials (RCTs) comparing ECP with or without alternative treatment versus alternative treatment alone in paediatric patients with chronic GvHD after haematopoietic stem cell transplantation.

Data collection and analysis

Two review authors independently performed the study selection. We resolved disagreements in the selection of trials by consultation with a third review author.

Main results

No additional studies were identified in this 2015 review update, in total leading to no studies meeting the criteria for inclusion in this review.

Authors' conclusions

The efficacy of ECP in the treatment of chronic GvHD in paediatric patients after haematopoietic stem cell transplantation based on RCTs cannot be evaluated since the original version of this review and the first review update found no RCTs. Current recommendations are based on retrospective or observational studies only. Thus, ideally, ECP should be applied in the context of controlled trials only. However, performing RCTs in this patient population will be challenging due to the limited number of patients, the variable disease presentation and the lack of well-defined response criteria. International collaboration, multicentre trials and appropriate funding for such trials will be needed. If treatment decisions based on clinical data are made in favour of ECP, patients should be carefully monitored for beneficial and harmful effects. In addition, efforts should be made to share this information with other clinicians, for example by setting up registries for paediatric patients that are treated with ECP.

PLAIN LANGUAGE SUMMARY

Extracorporeal photopheresis treatment for chronic graft-versus-host disease after haematopoietic stem cell transplantation in paediatric patients

Background

Chronic graft-versus-host disease is a common complication after haematopoietic stem cell transplantation (HSCT; transplant of blood-forming stem cells). Immune cells (white blood cells) from the donor recognise the patient's cells as foreign ('non-self'). Therefore, the transplanted immune cells attack the cells of the patient. The main affected organs are skin, liver and gut, among others. These immune reactions may cause acute inflammation (sudden swelling) followed by chronic (long-term) changes of organs (e.g. fibrosis; scarring of the lungs). First-line therapy usually consists of immunosuppressive drugs (which reduce the strength of the body's immune system) in the form of corticosteroids in combination with other immunosuppressive agents in refractory cases (where the disease is resistant to treatment). These drugs are supposed to suppress the immune-mediated attack of the patient's cells. Limited effectiveness and severe side effects of these drugs have led to the application of several alternative approaches.

Extracorporeal photopheresis (ECP) is an immunomodulatory therapy that involves collection of immune cells from peripheral blood outside the patient's body. These immune cells are exposed to a photoactive agent (a chemical that responds to exposure to light; e.g. 8-methoxypsoralen) with subsequent ultraviolet-A radiation and then re-infused. The immunomodulatory effects of this procedure have not been completely elucidated. Several current clinical practice recommendations suggest consideration of ECP in paediatric patients with chronic graft-versus-host disease.

Study characteristics

We searched scientific databases for randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) that were designed to evaluate the effectiveness and safety of ECP for the management of chronic graft-versus-host disease in children and adolescents (under 18 years of age) after HSCT.

Results

The original version of this review and this 2015 review update found no RCTs that analysed the efficacy of ECP for paediatric patients with chronic graft-versus-host disease after HSCT. Current recommendations are based on retrospective (a study in which the outcomes have occurred to the participants before the study began) or observational (a study in which the investigators do not seek to intervene, and simply observed the course of events) studies only. Thus, ideally, ECP should be applied in paediatric patients in the context of RCTs only. ECP may be considered in people with steroid-refractory chronic GvHD, keeping in mind that such a treatment is not supported by high-level evidence. If treatment decisions based on clinical data in favour of ECP are made, patients should be carefully monitored for beneficial and harmful effects and efforts should be made to share this information with other clinicians, for example by setting up registries for paediatric patients that are treated with ECP.

BACKGROUND

Description of the condition

Haematopoietic stem cell transplantation (HSCT) is a curative treatment option for children with haematological malignancies, haemoglobinopathies, immune deficiencies and inborn errors of metabolism (Diaconescu 2005; Gaziev 2010; Kennedy-Nasser 2006; Peters 2003; Rapoport 2011; Walters 2000; Walters 2005). Chronic graft-versus-host disease (cGvHD) is considered one of the major complications following HSCT, limiting its wider application (Billingham 1966; Ferrara 2004; Sullivan 2004). cGvHD was traditionally defined by manifestation after 100 days following HSCT (Gilman 2000). Several advances in the practice of HSCT (including different haematopoietic stem cell sources, intensity of conditioning regimen, immunosuppression and donor lymphocyte infusions) resulted in a more time variable presentation of cGvHD (Bunin 2008; Eapen 2004). Presently, cGvHD is described according to its pattern of presentation: following HSCT as a progression from acute graft-versus-host disease (aGvHD) (progressive form); as a recurrence after a disease-free interval (quiescent form); and without a history of aGvHD (de novo form) (Shulman 1988). The US National Institutes of Health (NIH) developed a diagnosis and scoring system defining cGvHD based on specific clinical signs and histopathology rather than time of onset after HSCT (Filipovich 2005; Jagasia 2009). The NIH global severity score uses a numerical scoring system for individual organs to calculate a summary scale according to the number and severity of organs involved. This provides a more clinically informative and discriminating severity measure for use in clinical trials and is an indicator for the necessity of systemic immunosuppressive treatment (Arai 2010).

The incidence of cGvHD varies between 6% and 65%, depending on the transplant procedure and disease-specific variables (Meisel 2007; Rocha 2000; Zecca 2002). Well-known risk factors for developing cGvHD are precedent aGvHD, stem cell donor, the preparative regimen, prophylactic procedures and the underlying disease (Flowers 2011; Rocha 2000; Zecca 2002). The exact pathogenesis of cGvHD remains unclear. Several studies demonstrated the role of T cells in the development of cGvHD (De Bueger 1993; Higman 2004; Mutis 1999). Increased levels of non-specific antibodies in people with cGvHD and response to B-cell-depleting antibodies suggest that B cells also play a role (Allan 2007; Zhang 2006). Moreover, a co-ordinated T-cell B-cell interaction to minor histocompatibility alloantigens seems to account for the manifestation of cGvHD (Miklos 2005). Soluble inflammation-associated factors are also involved in the pathogenesis of cGvHD (Fujii 2008; Lin 2003). Other pathogenetic suggestions include a defective negative selection of autoreactive T cells due to thymic damage, aberrant production of transforming growth factor-beta and activation of the platelet-derived growth factor receptor, as well as deficiency of CD8+ cells (Martin 2008; Toubai 2008). Clinical manifestations of cGvHD are separated into rather inflammatory, acute type features (erythematous rash, mucositis, diarrhoea, transaminitis and pulmonary infiltrates) as opposed to more fibrotic, chronic characteristics (sclerotic and lichen planus-like skin changes, fasciitis, sicca syndrome, oesophageal strictures and bronchiolitis obliterans) (Flowers 2002; Higman 2004). The most commonly affected organs, isolated or in combination, are the skin and oral cavity, with over 70% involvement for both, followed by eyes, liver, lungs, gastrointestinal tract and musculoskeletal system (Atkinson 1990; Beredjiklian 1998; Chosidow 1992; Cooke 2009;

Dudek 2003; Filipovich 2005; Janin 1994; Lee 2003; Melin-Aldana 2007; Pavletic 2005; Sullivan 1981; Treister 2005).

Both cGvHD and treatment of cGvHD lead to significant morbidity and mortality in children; however, outcome reports for cGvHD are mostly based on adult retrospective studies with a five-year overall survival rate of 60% to 90% in the low-risk range, 40% to 75% in the intermediate-risk range, and 10% to 60% in the high-risk range, using the previous grading and scoring system (Akpek 2003; Cahn 2005; Couriel 2006; Lee 2003; Shimada 2005). cGvHD accounts for 54% of deaths in adults two years after transplantation among the non-relapse-related deaths (Higman 2004; Horowitz 2004; Wingard 2002). The only available study with a larger cohort in children reports an overall six-year disease-free survival of 68% in the presence of cGvHD (Zecca 2002). According to reports in adults, immunosuppressive therapy is still required in 50% of people five years after the diagnosis of cGvHD (Stewart 2004).

Management options

Since aGvHD also has a significant impact on the pathogenesis of cGvHD, prophylaxis to prevent graft-versus-host disease (GvHD) plays a major role (Ram 2009). Prevention is based on T-cell inhibition including the following strategies: inhibition of T-cell activation and function (calcineurin inhibitor), inhibition of T-cell proliferation (methotrexate, mycophenolate mofetil) and elimination of T cells (alemtuzumab, anti-thymoglobulin) (Shah 2007; Storb 1986). The majority of children undergoing HSCT receive GvHD prophylaxis, starting before transplantation and typically continuing for up to six months after transplantation (Barrett 2008).

The clinical management of people with cGvHD is complicated due to the variability of disease manifestation, clinical course, infectious complications and treatment-related toxicity (Flowers 2002). Therefore, treatment of cGvHD in children is highly variable, and, due to lack of paediatric studies, mostly based on the experience in adults. In people with mild cGvHD and high-risk malignancies where a graft-versus-leukaemia effect gains importance, topical therapy should be considered (Filipovich 2005). Drug therapy for mild cGvHD mostly includes locally applied immunosuppressive agents (steroids and calcineurin inhibitors) for the affected organ (skin, eyes, oral cavity and lungs) (Jacobsohn 2010). In contrast, moderate-to-severe cGvHD is mostly treated with systemic steroids (Filipovich 2005; Salmasian 2010). Prednisone is usually tapered (alternate day) for the next two to three months (Sullivan 1988a). Some reports suggest better response rates and fewer corticosteroid complications when adding a calcineurin inhibitor (cyclosporin, tacrolimus) to systemic steroids (Koc 2002; Sullivan 1988b; Vogelsang 2001). Regarding the effect of corticosteroids on the growth and development of children and the mean duration of therapy of three years for people with cGvHD, the management of a daily calcineurin inhibitor with alternate day prednisone is considered standard for the treatment of cGvHD (Koc 2002; Sullivan 1988a). This therapeutic regimen yielded an objective response in more than 50% of people (Sullivan 1988a; Sullivan 1988b).

In cases where there is no response to therapy within four weeks, second-line treatment is mostly considered (Jacobsohn 2010). There are various salvage therapies including general immunosuppressants (mycophenolate mofetil, methotrexate, sirolimus, thalidomide, pentostatin and hydroxychloroquine) and monoclonal antibodies (rituximab) (Akpek 2001; Bolanos-Meade

2008; Busca 2000; Cutler 2006; Fraser 2007; Gilman 2006; Goldberg 2003; Jacobsohn 2009; Johnston 2005; Lopez 2005; Martin 2009; Mookerjee 1999; Vogelsang 1992).

Description of the intervention

Extracorporeal photopheresis (ECP), an immunomodulatory therapy, may play a role in the treatment of cGvHD. During ECP, peripheral mononuclear cells are collected ex vivo by leukapheresis, incubated with the photoactive and photosensitising drug 8-methoxypsoralen (8-MOP), exposed to ultraviolet-A (UV-A) light and then re-infused into the patient without any adverse effects to other organs (Betha 1999; Girardi 2002; Heald 1989). Psoralen occurs naturally in the seeds of the furocoumarin family of plants and its exposure to UV-A light (wavelength 200 to 350 nm) facilitates the intercalation of psoralen with deoxyribonucleic acid (DNA), leading to the formation of both monofunctional and bifunctional adducts, which results in programmed cell death (apoptosis) of the majority of cells (Yoo 1996). Initially, the patients received psoralen orally prior to the leukapheresis (Betha 1999). However, oral application results in an inconstant absorption of the drug and considerable gastrointestinal adverse effects (Brickl 1984). The now generally used ex vivo method, with the incubation of the collected cells in a bag, significantly reduces the exposure of the patient to 8-MOP (Schooneman 2003).

ECP has been successfully applied in the treatment of cutaneous T-cell lymphoma since the 1980s (Edelson 1987). Following this observation, the method has been implemented for a wider spectrum of immunologically mediated diseases such as systemic sclerosis, autoimmune disorders, solid organ rejection, aGvHD and cGvHD (Szodoray 2010). In the paediatric setting, many authors report a response rate of 33% to 93% to ECP as second-line treatment in steroid-resistant cGvHD (Foss 2005; Messina 2003; Smith 1998; Sniecinski 1994). People with steroid-refractory cGvHD that respond to ECP have a higher five-year survival rate compared with non-responders (96% with responders versus 85% with non-responders) (Perotti 2010). Adverse reactions are uncommon (less than 0.003%), transient and mild (nausea, hypotension, dizziness, cytopenia, skin infection at site of venous access and abnormal clotting to heparin) (Kanold 2003). Moreover, ECP is not associated with increased risk of systemic infections and relapse of malignant disease (Dall'Amico 2002; Hackstein 2009; Scarisbrick 2008).

How the intervention might work

The mechanisms of action of ECP are not completely understood. It has been shown that the procedure induces apoptosis in mononuclear white blood cells (Voss 2010). However, only a small percentage of the peripheral mononuclear cells is treated and, therefore, an immunomodulatory effect of the apoptotic cells is hypothesised (Heshmati 2003). One suspected mechanism is that apoptotic T-cell fragments presented by dendritic cells induce an anti-idiotypic T-suppressor activity, or downregulate a pre-existing T-cell response, and in this way generate a tolerogenic response and modulate cytokine production (Bladon 2006; Legitimo 2007; Xia 2009). In summary, the postulated mechanisms involved include: reduced stimulation of effector T cells, deletion of effector T cells, induction of regulatory T cells, increase of anti-inflammatory cytokines (i.e. tumour necrosis factor-beta, interleukin-10), and reduction of proinflammatory cytokines (interleukin-1beta, interleukin-6, and tumour necrosis

factor-alpha) (Fimiani 2004). On the basis of this hypothesis, photopheresis seems to downregulate the T-cell alloreactivity that plays the central role in the pathogenesis of GvHD after HSCT (Lamioni 2005; Maeda 2005).

Why it is important to do this review

cGvHD remains one of the major challenges for transplant-related morbidity and mortality after stem cell transplantation in paediatric patients. All conventional therapies, including established first-line therapy, have considerable adverse effects and probably increase the risk of infections and relapse of malignant disease. Therefore, it is essential to develop new therapeutic approaches for the selective immune control of cGvHD without generalised immunosuppression-related complications (infections and pharmacological toxicity issues) (Wolff 2011). ECP seems to be an effective immunomodulatory therapy with very mild, if any, adverse effects and, therefore, may be a promising alternative for improving morbidity and mortality in children with cGvHD.

The current review is the first update of the original review and protocol (Weitz 2012; Weitz 2014).

OBJECTIVES

To evaluate the effectiveness and safety of ECP for the management of cGvHD in children and adolescents after HSCT.

METHODS

Criteria for considering studies for this review

Types of studies

We intended to consider randomised controlled trials (RCTs) for this review if they assessed any clinical outcome as described in the [Types of outcome measures](#) section. For medical reasons (e.g. we did not consider cGvHD a stable condition), we aimed to include only trials with a parallel group design. We excluded studies restricted to adults (≥ 18 years of age). For studies including both children and adults, we planned to include studies if children represented more than 50% of participants in the study.

Types of participants

We planned to include children and adolescents under 18 years of age who underwent HSCT therapy with presence of cGvHD, independent of the underlying disease and donor source. We planned to consider all stages and grades of cGvHD, independent of the type of organ involvement.

Types of interventions

For the purpose of this review, we considered systemic steroids with or without calcineurin inhibitors as standard treatment as first-line therapy and considered all other treatment as second-line therapy of cGvHD.

The following comparisons for ECP for cGvHD after HSCT were conceivable.

- ECP versus standard treatment in paediatric patients with cGvHD as first-line treatment.
- ECP plus standard treatment versus standard treatment alone in paediatric patients with cGvHD as first-line treatment.

- ECP versus standard treatment in paediatric patients with steroid-/calcineurin-inhibitor-refractory cGvHD (second-line treatment).
- ECP plus standard treatment versus standard treatment alone in paediatric patients with steroid-/calcineurin-inhibitor-refractory cGvHD (second-line treatment).

These comparisons constituted four separate groups and we anticipated analysing them separately.

Types of outcome measures

Primary outcomes

- Response to ECP treatment (defined as either classical response rates (i.e. number of people in complete or partial remission) or percentage of achieved reduction in either NIH score (Filipovich 2005; Jagasia 2009), scales of Akpek and Lee (Akpek 2001; Lee 2003), or steroid-tapering under therapy with ECP (defined as number of people with at least 25% reduction in steroid dose).

Secondary outcomes

- Overall survival (defined as the time to death from any cause, starting at the day of HSCT).
- Failure-free survival (defined as progression of GvHD, expressed as change in NIH score or intensification of treatment, or both).
- Adverse events.
- Quality of life.
- Cost of intervention per month including length of hospital stay in days, number of outpatient attendances, direct medical resource use, direct medical costs, indirect medical resource use or costs and patient out-of-pocket expenses.

Search methods for identification of studies

We applied no language restrictions.

Electronic searches

The search for the original version of this review was done on 12 September 2012 in the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 9, 2012); MEDLINE/PubMed (1945 to 12 September 2012) and EMBASE (Ovid) (1980 to 12 September). The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are shown in Appendix 1; Appendix 2; and Appendix 3.

For the 2015 search update, we applied the same strategy without changes, from the date of the last search to 23 September 2015.

Searching other resources

Conference proceedings

We carried out an electronic search for the original version of this review using the regular search with keyword terms ("extracorporeal"; "photopheresis"; "photochemotherapy"; "psoralen"; "graft-versus-host") for the conference proceedings of the following societies on 12 September 2012.

- International Society for Paediatric Oncology (SIOP) (2007 to 2012).
- American Society of Clinical Oncology (ASCO): *Journal of Clinical Oncology* (1995 to 2012).

- American Society of Hematology (ASH): *Blood* (2001 to 2012).
- American Society of Blood and Marrow Transplantation: *Biology of Blood and Marrow Transplantation* (1990 to 2012).
- European Group for Blood and Marrow Transplantation (EBMT): *Bone Marrow Transplantation* (2000 to 2012).

We searched the reference lists of relevant articles and review articles.

We carried out a search update on 29 September 2015 without modifications, to cover conference proceedings from after the initial search date.

Electronic search in databases of ongoing trials

For the original version of this review, we searched the following clinical trials registries for ongoing or recently completed trials, and for locating potential links to other related databases and resources on 12 September 2012. Regular search with keywords ("extracorporeal"; "photopheresis"; "photochemotherapy"; "psoralen"; "graft-versus-host") was used where applicable, no time restrictions applied and the search not limited to trials involving children.

- ISRCTN registry (controlled-trials.com/).
- ClinicalTrials.gov (ClinicalTrials.gov).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch).
- Trials Central (www.trialscentral.org/) (search via "condition": "graft vs host disease").
- Internet Portal of the German Clinical Trials Register (DRKS) (www.drks.de/).
- NCIC Clinical Trials Group (www.ctg.queensu.ca/).
- National Cancer Institute (www.cancer.gov) (under heading "childhood cancers" and "cancers in childhood and adolescents" using "research" button).
- Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au/trialSearch.aspx).

For the 2015 update of this review, we repeated the initial search without modifications from the date of the last search to 29 September 2015.

Data collection and analysis

Selection of studies

The original review was undertaken by four review authors (MW, BS, FM, DB). One review author (MW) screened all titles and abstracts of the references identified by the search strategies for relevance. We only excluded citations that were clearly irrelevant at this stage. We considered citations as irrelevant that included only adults, were animal studies, did not describe cGvHD and that used stem cell sources other than haematopoietic. Two review authors (MW, DB) independently screened the remaining titles, excluded all irrelevant publications and recorded details of the studies together with the reasons for exclusion. We resolved any disagreement on the eligibility of studies through discussion and consensus. We obtained full-text versions of all potentially relevant papers. Two review authors (MW, DB) independently screened these manuscripts, identified potentially relevant studies and assessed eligibility of studies for inclusion. We resolved any disagreements on the eligibility of studies through discussion and consensus.

For this 2015 update, an additional author (MS) screened titles, abstracts and potentially relevant studies.

Data extraction and management

- We planned to extract data using a data extraction form developed by the review authors, and one of the review authors (MW) would transcribe the data into Review Manager 5 (RevMan 2014). Another review author (JM) was to verify all data entry for discrepancies. We planned to resolve any disagreements on data extraction and management issues through discussion and consensus, or if necessary through a third review author (DB or BS). We intended to request missing data from the original investigators.
- Two review authors (MW, JM) would have completed the 'Characteristics of included studies' table. Study characteristics would have included place of publication, date of publication, population characteristics, setting, detailed nature of intervention, detailed nature of comparator and detailed nature of outcomes. A key purpose of these data was to define unexpected clinical heterogeneity in included studies independently from analysis of results.
- Two review authors (MW, JM) intended to carefully record reasons why an included study did not contribute data on a particular outcome and to consider the possibility of selective reporting of results on particular outcomes.

Assessment of risk of bias in included studies

Two review authors (MW, DB) planned to assess independently each included study for risk of bias using the definitions for the different risk of bias items as stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and any other potential threats to validity (Higgins 2011; Kjaergard 2001; Moher 1998; Schulz 1995). We also planned to assess the risk of bias for blinding of outcome assessors and incomplete outcome data separately for each outcome. We aimed to consider a trial as having a low risk of bias if we assessed all domains as adequate. We planned to consider a trial as having a high risk of bias if we assessed one or more domain as inadequate or unclear. We wanted to report the 'Risk of bias' table as part of the 'Characteristics of included studies' table and present a 'Risk of bias' summary figure that would detail all of the judgements made for all included studies in the review (Higgins 2011). For each included study, we planned to assess selective reporting bias by comparing the methods and results section of the individual studies. We intended to resolve any disagreements on the assessment of risk of bias through discussion and consensus, or if necessary through a third review author (JM or BS) and to explore the impact of the level of bias through undertaking sensitivity analyses (see [Sensitivity analysis](#)).

Measures of treatment effect

We planned to analyse extracted data using Review Manager 5 (RevMan 2014).

We planned to extract hazard ratios (HR) with their 95% confidence intervals (CI) for time-to-event outcomes, such as mortality. If HRs were not provided, we intended to use the indirect estimation methods described in [Parmar 1998](#) and [Williamson](#)

2002 to calculate them. As an alternative, we intended to use the proportions of participants with the respective outcomes measured at certain time points to calculate risk ratios (RR).

We planned to express results for binary outcomes as RRs with 95% CIs as measures of uncertainty. For continuous outcomes, we planned to express the results as mean differences (MD), with 95% CIs as measures of uncertainty.

Unit of analysis issues

Since, for medical reasons, we only aimed to include parallel group randomised trials, unit of analysis issues related to cross-over and cluster randomised trials were not relevant for this systematic review. In the context of ECP, "body-part randomisation" and "body part analyses" did not make sense, so related issues do not need to be discussed here. In cases of parallel group designs with three or more treatment groups, we planned to divide the control group into several parts, so that the total number added up to the original size of the group.

Dealing with missing data

We planned to contact original investigators for missing data regarding study selection, data extraction and risk of bias assessment. To optimise the strategy for dealing with missing data, we intended to conduct an intention-to-treat analysis, which would have included all participants who did not receive the assigned intervention according to the protocol, as well as those who were lost to follow-up. If unsuccessful, we wanted to address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We planned to assess statistical heterogeneity using the I^2 statistic (Higgins 2002; Higgins 2003). This measure describes the percentage of total variation across studies that is caused by heterogeneity rather than by chance (Higgins 2003). The values of I^2 lie between 0% and 100%. We planned to use a simplified categorisation of heterogeneity with the following categories: low (I^2 less than 30%), moderate (I^2 between 30% and 60%) and high (I^2 more than 60%) (Deeks 2011).

If moderate or high heterogeneity had been detected, we intended to explore clinical heterogeneity by examining differences between groups as detailed below ([Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

We minimised the likelihood of publication bias by using a comprehensive search strategy without language restrictions and we also searched trial registries. In addition to the evaluation of reporting bias, as described in the [Assessment of risk of bias in included studies](#) section, we planned to assess reporting bias by constructing a funnel plot where a sufficient number of studies had been identified (i.e. at least 10 studies included in a meta-analysis). If there were fewer studies, the power of these tests would be too low to distinguish chance from real asymmetry (Sterne 2011).

Data synthesis

For future updates, we will conduct meta-analyses of pooled data from all contributing studies using Review Manager 5 (RevMan

2014). We intended to use a fixed-effect model as primary analysis. If we had found high clinical, methodological or statistical heterogeneity (I^2 more than 50%), we would, as a secondary analysis, have used a random-effects model and reported results from both models. We planned to summarise studies in cases where pooling of results was not possible.

Subgroup analysis and investigation of heterogeneity

We planned to assess clinical heterogeneity by examining differences due to:

- underlying disease;
- type of haematopoietic stem cell source;
- age of children at HSCT;
- age at start of ECP;
- type of conditioning regimen;
- type of GvHD prophylaxis regimen; and
- degree of human leukocyte antigen (HLA) compatibility (matched sibling donor versus matched unrelated donor versus mismatched unrelated donor).

Sensitivity analysis

We planned to investigate the robustness of our results through a sensitivity analysis on the basis of risk of bias of the included studies by defining the following groups:

- low risk of bias (adequate sequence generation and allocation concealment; successful blinding of all participants, care

providers and outcome assessors; incomplete outcome data for less than 20% of participants; no selective reporting or other sources of bias);

- high risk of bias (no adequate sequence generation and allocation concealment; no adequate blinding of all participants, care providers and outcome assessors; incomplete outcome data for more than 20% of participants; selective reporting or other sources of bias);
- unclear risk of bias (rating of unclear risk of bias in at least one of these seven categories).

We intended to perform sensitivity analyses for each risk of bias item separately.

RESULTS

Description of studies

We found no RCTs meeting the inclusion criteria for the original version of this review and its 2015 update (see: [Characteristics of excluded studies](#) table; [Characteristics of ongoing studies](#) table).

Results of the search

We performed the initial search on 12 September 2012. The search yielded 68 articles including three duplicates in CENTRAL, MEDLINE/PubMed and EMBASE (Ovid) ([Figure 1](#)). After title and abstract screening, we excluded 53 of the unique articles, as the intervention was not ECP.

Figure 1. Identification of potentially eligible studies.

We screened 12 full-text articles but we found only one RCT. However, this RCT was not eligible for inclusion in the review (see [Excluded studies](#)). We found another 11 studies by searching the references of the full-texts articles. In total, the 23 articles were not eligible and we excluded them following full-text screening. Reasons for exclusion were as follows:

- 13 were case report/case series;
- four were reviews reporting case reports/case series;
- four were prospective, not randomised, not controlled clinical trials;

- one was a retrospective case series;
- one was an RCT including less than 50% of children.

The search of the trial registers and conference proceedings identified no eligible studies. We contacted two experts in the field, which did not yield any studies.

We performed the latest search on 23 September 2015, yielding 20 new articles in CENTRAL, MEDLINE/PubMed, EMBASE (Ovid) and conference proceedings ([Figure 2](#)). After title and abstract screening, we excluded 15 of the unique articles for the following reasons:

Figure 2. Identification of potentially eligible studies for 2015 update.

- two were animal studies (mouse model);
- six were interventions other than ECP;
- one was a survey;
- one did not concern cGvHD;
- five were conference abstracts without references to published studies.

We screened five full-text articles but we found no RCTs to include in this review. We found a further five studies while searching the references of the full-text articles. These additional articles were also not eligible RCTs and we excluded them after abstract screening. Reasons for exclusion were as follows:

- four were case series;
- one was an RCT including no children.

The search of the trial registers (run 29 September 2015) identified no eligible studies.

Included studies

We found no RCTs in this 2015 review update meeting the inclusion criteria for this review.

Excluded studies

For this 2015 review update, we excluded additional data from two case series and three reviews.

See [Characteristics of excluded studies](#) table.

Risk of bias in included studies

We found no studies meeting the inclusion criteria for the original version of this review and its 2015 update. For that reason, the assessment of risk of bias was not applicable.

Effects of interventions

We found no studies meeting the inclusion criteria for this 2015 review update. For that reason the effectiveness and safety of ECP for the management of cGvHD in children and adolescents after HSCT remains unclear.

DISCUSSION

cGvHD remains one of the major challenges for transplant-related morbidity and mortality after HSCT in paediatric patients. ECP represents an alternative second-line treatment option in paediatric patients with cGvHD after HSCT. However, there were no data from RCTs available in the original version of this review and in the 2015 update to support or refute treatment with ECP in children with cGvHD after HSCT. Therefore, this systematic review cannot establish whether such a treatment is effective in paediatric patients with cGvHD after HSCT.

We limited the search strategy to children and adolescents under 18 years of age. However, we found one RCT during the initial 2014 review that assessed the efficacy of ECP in cGvHD in mainly adults (greater than 50%). This randomised controlled, single-blinded trial investigated the effect of ECP on the cutaneous manifestation of cGvHD in people with failed corticosteroid treatment following HSCT (Flowers 2008). People were eligible in case of: corticosteroid refractoriness defined as lack of response or disease progression after administration of a least 1 mg/kg of methylprednisolone equivalent, corticosteroid-dependency after more than 10 mg of methylprednisolone equivalent to control skin manifestation, and corticosteroid intolerance due to intolerable adverse effects. Steroids had to be applied in a stable dose for at least two weeks prior to randomisation and had to be maintained on the same dose level for the first six study weeks (with the exception of reduction due to adverse effects). Immunosuppressants such as tacrolimus, mycophenolate and ciclosporin A were accepted as concomitant medication if they had been introduced at least four weeks before randomisation. Discontinuation of these agents during the study

period was only permitted for safety reasons. The primary objective of the study was the median percentage change of total skin score (TSS) at week 12 compared with the pretreatment value. Secondary objectives included: the proportion of participants with at least 25% improvement in TSS, 50% or greater reduction in daily steroid dose compared with the baseline dose, or improvement of at least 25% in TSS in conjunction with steroid-sparing at weeks 12 and 24. Skin assessments were performed on alternate weeks up to study week 12 and afterwards on alternate weeks up to study week 24. Participants were randomised with a block scheme in a 1 : 1 ratio to the conventional therapy arm (49 participants) or to the conventional therapy arm combined with ECP (50 participants). Conventional therapy consisted of corticosteroids and other immunosuppressive agents in refractory participants. ECP was administered three times during week one, and then twice weekly on consecutive days during weeks two to 12. Responding participants could continue ECP treatment until week 24 following the schedule of two treatments every week. Ten participants (four in the study group, six in the control group) withdrew consent prior to study week 12. Four participants died due to multiple organ failure, cardiac failure and infection. The changes in TSS from baseline until week 12 between the ECP group (-14.5%) and the control group (-8.5%) were not statistically different. However, ECP-treated participants had a 50% or greater reduction in the total daily dose of corticosteroids. At week 12, the percentage of participants experiencing both a 50% or greater reduction in daily corticosteroid dose and a 25% or greater improvement in the TSS was higher in the ECP group (8%) than the control group (0%). Regarding TSS, 40% of the participants in the ECP group had a complete or partial skin response compared with 10% in the control group. Current clinical practice guidelines already recommend consideration of ECP as second-line therapy option in adults and paediatric patients with cGvHD based on the available and partially limited evidence (Wolff 2011). This 2015 review update found no further RCTs on ECP treatment in cGvHD patients.

Apart from this RCT, which enrolled mainly adults, the search strategy applied for the initial 2014 review identified 21 non-randomised, paediatric studies including several case reports, case series and observational studies that suggest a benefit of ECP in paediatric patients with cGvHD. We identified one major non-randomised, non-controlled prospective study including children with aGvHD (33 participants) and cGvHD (44 participants) resistant to conventional immunosuppressive therapy (Messina 2003). Depending on the original disorder and haematopoietic stem cell source, immunosuppressive prophylaxis consisted either of ciclosporin A alone, short-term methotrexate plus rabbit anti-thymoglobulin (ATG) or ciclosporin A combined with steroids. People with cGvHD and skin involvement were assessed according to the extent of skin surface involved (per cent ESS) and skin severity score (SSS) in monthly intervals. The clinical stage in people with organ involvement was graded for each organ and then combined to an overall grade following published criteria (Ferrara 1991; Przepiorka 1995; Sullivan 1991). Resistance to conventional immunosuppressive therapy after complete remission was defined as lack of clinical stabilisation or improvement after treatment with prednisolone at a dosage of 2.5 mg/kg for at least seven days and no response to at least two lines of alternative immunosuppressive treatment options (such as ciclosporin A or tacrolimus). The median Lansky/Karnofsky performance score at the start of the ECP was 60% (range 30% to 90%). Photopheresis was carried out on two consecutive days weekly for the first month, every two weeks

for the second and third month, followed by monthly intervals for at least three months. Clinical evaluation of the participants was done at months one, two, three and six after initiation of ECP. Complete response was defined as clinical stage 0 or I, partial response as improvement greater than 50% and no response as stable or progressive disease or improvement less than 50%. For the participants with cGvHD, the median Lansky/Karnofsky score improved from 60% to 90% (range 60% to 100%). About 59% of the participants had an overall improvement evaluated according to organ involvement. The median improvement in ESS was 26% and SSS scores was 8 points. At the end of ECP treatment, 44% of participants had a complete response; 29% a partial response; 5% no response; and 10 participants died due to complication of GvHD, infection or relapse of the primary disease. Participants with cGvHD responding to ECP had a significantly better five-year overall survival of 96.1% (95% CI 88.7% to 100%) compared with non-responders with 58.4% (95% CI 34.5% to 82.4%). The five studies identified during the 2015 review update were non-randomised and retrospective or summarised studies that did not meet the search criteria.

The presented studies provided only limited evidence for the efficacy of ECP in paediatric patients with cGvHD after HSCT and, therefore, should not solely be used to establish recommendations in paediatric patients. It is questionable if insights gained from data of the RCT performed in a predominantly adult population can be transferred to children (Flowers 2008). Further evaluation in controlled trials, preferably in RCTs, including cost-effectiveness analyses is urgently needed. However, performing RCTs in this age group will be challenging due to the limited number of children, the variable disease presentation and the lack of well-defined response criteria. International multicentre trials with appropriate funding will be needed to study the efficacy of ECP in cGvHD in children after HSCT. As of this 2015 review update, there is still no ongoing prospective RCT investigating the efficacy of ECP in people with cGvHD after HSCT to help to define the role of ECP in treatment of cGvHD in children and adolescents.

AUTHORS' CONCLUSIONS

Implications for practice

There is no randomised evidence for the use of extracorporeal photopheresis (ECP) in paediatric patients with chronic graft-versus-host disease (cGvHD) after haematopoietic stem cell transplantation (HSCT). During the course of this review, we identified case reports, case series and observational studies. Thus, ideally, ECP should be applied in paediatric patients in the context of randomised controlled trials (RCTs) only and international efforts should be undertaken to set up such a study. There is no high-quality evidence to support the use of ECP in people with steroid-refractory cGvHD.

Implications for research

Future RCTs will need the incorporation of: reliable and validated scoring systems to assess disease manifestations; well-defined response criteria; and relevant outcome measures including overall survival, failure-free survival, adverse effects, quality of life, long-term effects and cost-effectiveness analyses. Furthermore, the efficacy of ECP may depend on the affected organ system and a subgroup analysis according to disease manifestation will help to clarify this issue. Furthermore, the type of photopheresis

procedure should be specified. Once the value of ECP is established, comparative trials defining the advantages and disadvantages of the various ECP regimens should be considered while keeping in mind that the performance of such RCTs is very challenging and may incorporate methodological design issues for rare diseases. If treatment decisions based on clinical grounds in favour of ECP are made, patients should carefully be monitored for beneficial and harmful effects and efforts should be made to share this information with other clinicians, for example by setting up registries for paediatric patients that are treated with ECP.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abu-Dalle 2014	Review article reporting on efficacy of ECP for aGvHD and cGvHD treatment
Apisarnthanarax 2003	Retrospective study on 2 paediatric patients and 62 adults with cGvHD
Balda 1996	Case report of 1 child with cGvHD
Besnier 1997	Case series of 3 paediatric patients and 4 adults with aGvHD (2 children) and cGvHD (5 children)
Biagi 2000	Case report of paediatric patients with cGvHD
Bisaccia 2011	Case report of paediatric patient with cGvHD
Bruserud 2014	Review article reporting on results from clinical studies of ECP treatment in aGvHD and cGvHD
Child 1999	Case series of 11 adults with cGvHD
D'Incan 2000	Case series of 3 paediatric patients with GvHD
Dall'Amico 1997	Case series of 4 paediatric patients with cGvHD
Das-Gupta 2014	Retrospective, uncontrolled study on 128 patients (less than 50% paediatric) with aGvHD
Dhir 2014	Review article reporting on pathobiology of cGvHD/aGvHD, biomarker development and treatment strategies
Flowers 2008	Multicentre prospective phase 2 randomised controlled study in people with cGvHD including less than 50% children
Foss 2003	Review reporting case series
Foss 2005	Study not randomised, not controlled. Prospective, single-arm study of 23 adults and 2 children with chronic cutaneous or visceral GvHD
Halle 2002	Case series of 8 paediatric patients with cGvHD
Jagasia 2013	Retrospective study on 98 patients (less than 50% paediatric) with aGvHD
Kanold 2003	Case series of paediatric patients with cGvHD
Kanold 2005	Review article reporting case series of paediatric patients with aGvHD or cGvHD treated with ECP

Study	Reason for exclusion
Kanold 2007	Prospective, not randomised, study in paediatric patients with aGvHD or cGvHD treated with ECP
Looks 1996	Case report of paediatric patient with aGvHD
Messina 2003	Prospective, not randomised, uncontrolled study of 77 paediatric patients with acute (33 children) or chronic (44 children) immunosuppressive-resistant GvHD
Perotti 1999	Prospective, not randomised, uncontrolled study in paediatric patients with aGvHD (1 child) and cGvHD (6 children)
Peters 2000	Review article reporting different therapeutic options for GvHD
Rossetti 1995	Case report of 1 child with cGvHD
Rossetti 1996	Case series of 9 paediatric patients with aGvHD (1 child) and cGvHD (8 children)
Salvaneschi 2001	Case series of 9 children with aGvHD and 13 children with cGvHD
Zecca 2000	Review article reporting different therapeutic options for GvHD

aGvHD: acute graft-versus-host disease; cGvHD: chronic graft-versus-host disease; ECP: extracorporeal photopheresis; GvHD: graft-versus-host disease.

APPENDICES

Appendix 1. Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL)

- For **Stem cell transplantation**, we used the following text:

stem cell transplantation OR stem cell transplantations OR SCT OR hematopoietic stem cell transplantation OR HSCT OR peripheral blood stem cell transplantation OR peripheral stem cell transplantation OR PBSCT OR stem cell OR stem cells OR stem cell* OR bone marrow transplantation OR BMT OR hematopoietic stem cell mobilization OR hematopoietic stem cell mobilisation OR allograft OR allografts OR allograft* OR allogeneic transplantation OR allogeneic marrow transplantation OR allogeneic* OR homologous transplantation OR myeloablative therapy OR myeloablative agonist OR myeloablative agonists OR myeloablative* OR mega therapy OR high-dose therapy OR high dose therapy OR stem cell rescue OR bone marrow rescue OR bone marrow grafting OR bone marrow cell transplantation OR cord blood stem cell transplantation OR placental blood stem cell transplantation OR umbilical cord stem cell transplantation

- For **Graft-versus-host disease**, we used the following text words:

graft versus host disease OR graft vs host disease OR chronic graft versus host disease OR chronic graft vs host disease OR acute graft versus host disease OR acute graft vs host disease OR GVHD OR cGVHD OR aGVHD OR graft versus leukemia OR graft vs leukemia OR homologous wasting disease OR graft versus host reaction OR graft vs host reaction

- For **Photopheresis**, we used the following text words:

photopheresis OR extracorporeal photopheresis OR Photopheresis, Extracorporeal OR Photochemotherapy, Extracorporeal OR ECP OR Extracorporeal Photochemotherapy OR Extracorporeal Photochemotherapies OR Photochemotherapies, Extracorporeal OR photochemotherapy OR photodynamic therapy OR photodynamic therapies OR phototherapy OR PDT OR phototherapies OR ultraviolet therapy OR ultraviolet therapies OR UVA-irradiation OR photoradiation OR ficusin OR psoralene OR psoralen OR psoralens OR 66-97-7 OR 8-methoxypsoralen OR 8-MOP OR 8MOP OR 8 MOP OR Methoxsalen OR 298-81-7 OR photochemical OR photochemicals OR photosensitizer* OR photosensitiser*

- For **Children**, we used the following text words:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR

prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy

Final search 1 AND 2 AND 3 AND 4

The search was performed in title, abstract or keywords.

Appendix 2. Search strategy for MEDLINE/PubMed

- For **Stem cell transplantation**, we used the following MeSH headings and text words:

stem cell transplantation OR stem cell transplantations OR SCT OR hematopoietic stem cell transplantation OR HSCT OR peripheral blood stem cell transplantation OR peripheral stem cell transplantation OR PBSCT OR stem cell OR stem cells OR stem cell* OR bone marrow transplantation OR BMT OR hematopoietic stem cell mobilization OR hematopoietic stem cell mobilisation OR allograft OR allografts OR allograft* OR allogeneic transplantation OR allogeneic marrow transplantation OR allogeneic* OR homologous transplantation OR myeloablative therapy OR myeloablative agonist OR myeloablative agonists OR myeloablative* OR mega therapy OR high-dose therapy OR high dose therapy OR stem cell rescue OR bone marrow rescue OR bone marrow grafting OR bone marrow cell transplantation OR cord blood stem cell transplantation OR placental blood stem cell transplantation OR umbilical cord stem cell transplantation

- For **Graft-versus-host disease**, we used the following MeSH headings and text words:

graft versus host disease OR graft vs host disease OR chronic graft versus host disease OR chronic graft vs host disease OR acute graft versus host disease OR acute graft vs host disease OR GVHD OR cGVHD OR aGVHD OR graft versus leukemia OR graft vs leukemia OR homologous wasting disease OR graft versus host reaction OR graft vs host reaction

- For **Photopheresis**, we used the following MeSH headings and text words:

photopheresis OR extracorporeal photopheresis OR Photopheresis, Extracorporeal OR Photochemotherapy, Extracorporeal OR ECP[tiab] OR Extracorporeal Photochemotherapy OR Extracorporeal Photochemotherapies OR Photochemotherapies, Extracorporeal OR photochemotherapy OR photodynamic therapy OR photodynamic therapies OR phototherapy OR PDT[tiab] OR phototherapies OR ultraviolet therapy OR ultraviolet therapies OR UVA-irradiation OR photoradiation OR ficusin OR psoralene OR psoralen OR psoralens OR 66-97-7 OR 8-methoxypsoralen OR 8-MOP OR 8MOP OR 8 MOP OR Methoxsalen OR 298-81-7 OR photochemical OR photochemicals OR photosensitizer* OR photosensitiser*

- For **Children**, we used the following MeSH headings and text words:

infant OR infan* OR newborn OR newborn* OR new-born* OR baby OR baby* OR babies OR neonat* OR child OR child* OR schoolchild* OR schoolchild OR school child OR school child* OR kid OR kids OR toddler* OR adolescent OR adoles* OR teen* OR boy* OR girl* OR minors OR minors* OR underag* OR under ag* OR juvenil* OR youth* OR kindergar* OR puberty OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatrics OR pediatric* OR paediatric* OR peadiatric* OR schools OR nursery school* OR preschool* OR pre school* OR primary school* OR secondary school* OR elementary school* OR elementary school OR high school* OR highschool* OR school age OR schoolage OR school age* OR schoolage* OR infancy OR schools, nursery OR infant, newborn

- For **Randomised controlled trials (RCTs)/clinical controlled trials (CCTs)**, we used the following MeSH headings and text words:

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND humans[mh]

Final search: 1 AND 2 AND 3 AND 4 AND 5

[pt = publication type; tiab = title, abstract; sh = subheading; mh = MeSH term; * = zero to many characters; RCT = randomized controlled trial; CCT = controlled clinical trial]

Appendix 3. Search strategy for EMBASE (Ovid)

- For **Stem cell transplantation**, we used the following Emtree terms and text words:

- exp stem cell transplantation/
- (stem cell transplantation or stem cell transplantations or SCT).mp.
- exp hematopoietic stem cell transplantation/
- (hematopoietic stem cell transplantation or HSCT).mp.
- exp peripheral blood stem cell transplantation/
- (peripheral blood stem cell transplantation or PBSCT).mp.
- exp stem cell/
- (stem cell or stem cells or stem cell\$).mp.

9. exp bone marrow transplantation/
10. (bone marrow transplantation or BMT).mp.
11. exp stem cell mobilization/
12. (hematopoietic stem cell mobilization or hematopoietic stem cell mobilisation).mp.
13. exp allograft/
14. (allograft or allografts or allograft\$).mp.
15. exp allotransplantation/
16. (allogeneic transplantation or allogeneic marrow transplantation).mp.
17. allograft\$.mp.
18. homologous transplantation.mp.
19. myeloablative therapy.mp.
20. exp myeloablative agent/
21. (myeloablative agent or myeloablative agonists).mp.
22. myeloablative\$.mp.
23. (mega therapy or high-dose therapy or high dose therapy).mp.
24. exp bone marrow rescue/
25. (stem cell rescue or bone marrow rescue).mp.
26. bone marrow grafting.mp.
27. bone marrow cell transplantation.mp.
28. exp cord blood stem cell transplantation/
29. (cord blood stem cell transplantation or placental blood stem cell transplantation or umbilical cord stem cell transplantation).mp.
30. or/1-29

- For **Graft-versus-host disease**, we used the following Emtree terms and text words:

1. exp graft versus host reaction/
2. (graft versus host disease or graft vs host disease).mp.
3. exp chronic graft versus host disease/
4. (chronic graft versus host disease or chronic graft vs host disease).mp.
5. exp acute graft versus host disease/
6. (acute graft versus host disease or acute graft vs host disease).mp.
7. (GVHD or cGVHD or aGVHD).mp.
8. exp graft versus leukemia effect/
9. (graft versus leukemia or graft vs leukemia).mp.
10. homologous wasting disease.mp.
11. (graft versus host reaction or graft vs host reaction).mp.
12. or/1-11

- For **Photopheresis**, we used the following Emtree terms and text words:

1. PUVA/
2. (photopheresis or extracorporeal photopheresis).mp.
3. (Extracorporeal Photochemotherapy or Extracorporeal Photochemotherapies or ECP).mp.
4. photochemotherapy.mp. or exp photochemotherapy/
5. exp photodynamic therapy/
6. (photodynamic therapy or photodynamic therapies).mp.
7. exp phototherapy/
8. (phototherapy or phototherapies or PDT).mp.
9. (ultraviolet therapy or ultraviolet therapies).mp.
10. exp ultraviolet radiation/ or exp ultraviolet A radiation/
11. UVA-irradiation.mp.
12. photoradiation.mp.
13. exp psoralen/
14. (ficusin or psoralene or psoralen or psoralens).mp.
15. 66-97-7.rn.
16. exp methoxsalen/
17. (8-methoxypsoralen or 8-MOP or 8MOP or 8 MOP or Methoxsalen).mp.
18. 298-81-7.rn.
19. (photochemical or photochemicals).mp.
20. exp photosensitizing agent/
21. (photosensitizer\$ or photosensitiser\$).mp.
22. or/1-21

- For **Children**, we used the following Emtree terms and text words:

- infant/ or infancy/ or newborn/ or baby/ or child/ or preschool child/ or school child/
- adolescent/ or juvenile/ or boy/ or girl/ or puberty/ or prepuberty/ or pediatrics/
- primary school/ or high school/ or kindergarten/ or nursery school/ or school/
- or/1-3
- (infant\$ or newborn\$ or (new adj born\$) or baby or baby\$ or babies or neonate\$ or perinat\$ or postnat\$).mp.
- (child\$ or (school adj child\$) or schoolchild\$ or (school adj age\$) or schoolage\$ or (pre adj school\$) or preschool\$).mp.
- (kid or kids or toddler\$ or adoles\$ or teen\$ or boy\$ or girl\$).mp.
- (minors or minors\$ or (under adj ag\$) or underage\$ or juvenil\$ or youth\$).mp.
- (puber\$ or pubescen\$ or prepubescen\$ or prepubert\$).mp.
- (pediatric\$ or paediatric\$ or peadiatric\$).mp.
- (school or schools or (high adj school\$) or highschool\$ or (primary adj school\$) or (nursery adj school\$) or (elementary adj school) or (secondary adj school\$) or kindergar\$).mp.
- or/5-11
- 4 or 12

- For **Randomised controlled trials (RCTs)/clinical controlled trials (CCTs)**, we used the following Emtree terms and text words:

- Randomized Controlled Trial/
- Controlled Clinical Trial/
- randomized.ti,ab.
- placebo.ti,ab.
- randomly.ti,ab.
- trial.ti,ab.
- groups.ti,ab.
- drug therapy.sh.
- or/1-8
- Human/
- 9 and 10

Final search 1 and 2 and 3 and 4 and 5

[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; sh = subject heading; ti,ab = title, abstract; / = Emtree term; \$=zero or more characters ; RCT = randomized controlled trial; CCT = controlled clinical trial]

WHAT'S NEW

Date	Event	Description
23 September 2015	New citation required but conclusions have not changed	No new studies could be included in the review. As a result the conclusions have not changed.
23 September 2015	New search has been performed	The search for eligible studies was updated to September 2015.

CONTRIBUTIONS OF AUTHORS

Marcus Weitz: conception, design and co-ordination of the review. Identifying potential studies meeting the inclusion criteria (both by initial screening of the titles and abstracts and by screening of the full-text articles), data management and interpretation of the data. Writing of the review and approval of the final version.

Brigitte Strahm: interpretation of the data, clinical expertise, providing general advice on the review and approval of the final version.

Joerg Meerpohl: methodological support, identifying potential studies meeting the inclusion criteria (both by initial screening of the titles and abstracts and by screening of the full-text articles), data management and interpretation, and general advice on the review. Approval of the final version.

Maria Schmidt: identifying potential studies meeting the inclusion criteria (both by initial screening of the titles and abstracts and by screening of the full-text articles), data management and interpretation of the data. Writing of the review and approval of the final version.

Dirk Bassler: identifying potential studies meeting the inclusion criteria (both by initial screening of the titles and abstract and by screening of the full-text articles), data management and interpretation of data. Involvement in writing the review and approval of the final version.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No source of support, Other.

External sources

- No source of support, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Chronic Disease; Graft vs Host Disease [*therapy]; Hematopoietic Stem Cell Transplantation [*adverse effects]; Photopheresis [*methods]

MeSH check words

Adolescent; Child; Humans