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Jagannath VA, Fedorowicz Z, Al Hajeri A, Sharma A.
Hematopoietic stem cell transplantation for people with β -thalassaemia major.
Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD008708.
DOI: [10.1002/14651858.CD008708.pub4](https://doi.org/10.1002/14651858.CD008708.pub4).

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[Intervention Review]

Hematopoietic stem cell transplantation for people with β -thalassaemia major

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Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 11, 2016.

Citation: Jagannath VA, Fedorowicz Z, Al Hajeri A, Sharma A. Hematopoietic stem cell transplantation for people with β -thalassaemia major. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD008708. DOI: [10.1002/14651858.CD008708.pub4](https://doi.org/10.1002/14651858.CD008708.pub4).

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ABSTRACT

Background

Thalassemia is an inherited autosomal recessive blood disorder, caused by mutations in globin genes or their regulatory regions. This results in a reduced rate of synthesis of one of the globin chains that make up haemoglobin. In β -thalassaemia major there is an underproduction of β -globin chains combined with excess of free α -globin chains. The excess free α -globin chains precipitate in red blood cells, leading to their destruction (haemolysis) and ineffective erythropoiesis. The conventional approach to treatment is based on the correction of haemoglobin status through regular blood transfusions and iron chelation therapy for iron overload. Although conventional treatment has the capacity to improve the quality of life of people with β -thalassaemia major, allogeneic hematopoietic stem cell transplantation is the only currently available procedure which has the curative potential. This is an update of a previously published Cochrane Review.

Objectives

To evaluate the effectiveness and safety of different types of allogeneic hematopoietic stem cell transplantation, in people with severe transfusion-dependant β -thalassaemia major, β -thalassaemia intermedia or $\beta^0/\pm$ thalassaemia variants requiring chronic blood transfusion.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Haemoglobinopathies Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Date of the most recent search: 18 August 2016.

Selection criteria

Randomised controlled trials and quasi-randomised controlled trials comparing allogeneic hematopoietic stem cell transplantation with each other or with standard therapy (regular transfusion and chelation regimen).

Data collection and analysis

Two review authors independently screened studies and had planned to extract data and assess risk of bias using standard Cochrane methodologies but no studies were identified for inclusion.

Main results

No relevant studies were retrieved after a comprehensive search of the literature.

Authors' conclusions

We were unable to identify any randomised controlled trials or quasi-randomised controlled trials on the effectiveness and safety of different types of allogeneic stem cell transplantation in people with severe transfusion-dependant β -thalassaemia major or $\beta 0/+$ -thalassaemia variants requiring chronic blood transfusion. The absence of high-level evidence for the effectiveness of these interventions emphasises the need for well-designed, adequately-powered, randomised controlled clinical trials.

PLAIN LANGUAGE SUMMARY

Transplantation of blood-forming stem cells for people with β -thalassaemia major

Review question

We reviewed the evidence about the effect and safety of different types of allogeneic stem cell transplantation in people with severe transfusion-dependant β -thalassaemia major or $\beta 0/+$ -thalassaemia variants requiring chronic blood transfusion.

Background

Thalassaemia is a blood disorder passed down through families (inherited) in which the body is unable to make adequate amount of normal haemoglobin (the protein in red blood cells that carries oxygen). The disorder results in excessive destruction of red blood cells, which, without blood transfusions, leads to anaemia and causes significant mortality and morbidity. The anaemia can be treated effectively with regular blood transfusions. However, these lead to the accumulation of iron, which, unless treated with regular iron chelation, causes multiorgan disease and early death. Although β -thalassaemia major responds to this conventional treatment to correct haemoglobin status, the treatment does not provide a cure. The use of hematopoietic (blood-forming) stem cell transplantation involves replacing the unhealthy hematopoietic stem cells with normal hematopoietic stem cells from a healthy donor. These stem cells then produce normal red blood cells containing normal amounts of globin chains. Stem cells can be derived from either the bone marrow or blood (umbilical cord blood or peripheral blood) of a healthy individual.

Search date

The evidence is current to: 18 August 2016.

Key results

The review authors did not find any randomised controlled trials assessing the effectiveness and safety of different types of stem cell transplantation in people with severe transfusion-dependant β -thalassaemia major or $\beta 0/+$ -thalassaemia variants requiring chronic blood transfusion.

BACKGROUND

Description of the condition

Thalassemia is an autosomal recessively inherited blood disorder caused by mutations in globin genes or their regulatory regions. These mutations result in a reduced rate of synthesis of one of the globin chains that makes up haemoglobin. In β -thalassaemia major there is an underproduction of β -globin chains combined with excess of free α -globin chains. The excess free α -globin chains precipitate in the red blood cells (RBC) leading to their destruction (haemolysis) and ineffective erythropoiesis (Weatherall 2002). These people invariably suffer from mild to severe anaemia (low haemoglobin) and the effects that it causes on the various organs. The conventional approach to treatment is based on the correction of haemoglobin level through regular blood transfusions. Iron chelation therapy is required for the subsequent iron overload that occurs mainly due to chronic blood transfusions (transfusional haemosiderosis) and to a small extent due to increased intestinal iron absorption which is secondary to inhibition of hepcidin synthesis (Atanasiu 2007).

Thalassemias are particularly common among people of Mediterranean origin, with the highest prevalence of the disease found in Greece, parts of Italy, Portugal and in Spain. People of Arab and Asian descent may also be affected and the Maldives has the highest prevalence figures of thalassaemia in the world, with a carrier rate of 18% of the population. Further data indicate that thalassaemia affects 16% of people in Cyprus, 1% in Thailand and 3% to 8% in populations from Bangladesh, China, India, Malaysia and Pakistan (Angastiniotis 1998; Charafeddine 2008; Lau 1997). The actual number of people suffering from thalassaemia is unknown due to its high prevalence in less developed countries; in particular in the Middle East and Asia, where genetic screening resources are often very limited. Approximately 150 million people worldwide carry mutations in β -globin genes (Modell 2008) and over two million people with β -thalassaemia major requiring transfusions globally (Weatherall 2002).

Diagnosis is made through a combination of clinical manifestation, typical morphology of RBCs in a peripheral blood smear examination, electrophoresis or chromatography of the haemoglobin chains and by molecular detection of specific genetic mutations.

Children with β -thalassaemia major usually become symptomatic between six and 12 months of age. It is characterised by severe anaemia and enlargement of the liver and spleen due to extra-medullary hematopoiesis (formation of blood cells from locations other than bone marrow) (Olivieri 1999). It is a progressively debilitating disease which can involve multiple organs and is frequently associated with significant morbidity and mortality. It requires periodic blood transfusions and iron chelation; which are expensive life-long treatments. Without blood transfusions, people with β -thalassaemia major may develop massive bone marrow or extra-medullary hematopoiesis which can contribute to a range of morbidities, e.g. deformities of the facial bones, spinal cord compression and pathological fractures. Frequent transfusions pose a risk of iron overload complications such as hepatitis, liver fibrosis and cardiac disease which can also worsen the course of β -thalassaemia major (Dogramaci 2009; Olivieri 1999; Weatherall 2002).

Description of the intervention

While conventional treatment has the capacity to improve the quality of life of people with β -thalassaemia major, allogeneic hematopoietic stem cell transplantation (HSCT) is the only currently available procedure which has curative potential. In this procedure, progenitor cells (stem cells which mature into blood cells) are administered to an individual. The type of procedure is typically categorized based on the source of progenitor cells used in the transplant.

Three main sources of cells are available:

- the recipient (an autologous transplant);
- someone other than the recipient (an allogeneic transplant); or
- donated umbilical cord blood (a cord blood or umbilical cord blood transplant (UCB)).

The traditional source of hematopoietic stem cells for use in allogeneic transplantations used to be bone marrow. The use of peripheral blood as a source of these cells has lately replaced bone marrow for a significant proportion of allogeneic transplantations (Schrier 2005). Extensive evaluation of the recipient's disease status in addition to donor matching is required prior to transplantation (LHSC 2003). The ideal donor is a sibling who does not have thalassaemia is a match in human leucocyte antigen (HLA) type. The donor could be an HLA-identical related donor or HLA-matched unrelated donor (Petersdorf 2004).

Regimens of high doses of chemotherapy or chemo-radiotherapy are used to ablate recipient hematopoietic cells and to prevent graft rejection. Immunosuppression is administered for prevention and treatment graft versus host disease. After completion of preparatory conditioning, the stem cells are delivered to the recipient through an intravenous (IV) line as with a blood transfusion. The stem cells travel to the bone marrow and within two to four weeks after transplantation they begin to produce new white blood cells, red blood cells and platelets (engraftment).

Adverse events associated with the transplant procedure include risk of life-threatening infections, graft versus host disease (GVHD), graft rejection and recurrence of β -thalassaemia major (graft failure). Long-term morbidities associated with the procedure include solid organ tumours, infertility, gonadal failure, psychological disturbances and employment-related problems (Di Bartolomeo 2008). Reduced intensity preparative regimens may be used to decrease transplant related morbidity but unfavourable outcomes, such as graft rejection, are associated with reduced intensity conditioning regimens (Iannone 2003; Jacobsen 2004; van Besien 2000).

Although the autologous stem cell source is not generally applicable for transplants in thalassemias, the transfer of a regulated beta-globin gene in autologous HSCs, i.e. gene therapy, is an attractive potential treatment option for people with beta-thalassaemia (Sadelain 2005). Current investigation trials are focusing on optimising vector production methodologies and tackling safety issues with this modality (Bank 2005; Nienhuis 2008). A few individuals have been enrolled in phase 1 studies using this approach and long term outcomes are awaited. This approach avoids the complications related to GVHD and donor availability that are involved with conventional HSC transplantation.

How the intervention might work

Hematopoietic stem cell transplantation replaces the ineffective erythropoiesis with an effective allogeneic substitute. The transplanted hematopoietic progenitor cells take over the function and synthesise normal RBCs. This ongoing production of normal RBCs provides a curative solution for the haemolytic anaemia and freedom from the regular transfusion regimens and its associated pathologies such as iron overload.

Why it is important to do this review

Over the last two decades conventional therapy has improved the prognosis of thalassaemia; however, it continues to be a highly prevalent disease in many parts of the world and is often accompanied by numerous treatment-related complications.

The first stem cell transplant that successfully cured β -thalassaemia major was performed in 1982 (Thomas 1982) and since then a number of centres have explored this approach as a curative option (Lucarelli 1999; Lucarelli 2008). This procedure is now considered an acceptable form of treatment for people suffering with β -thalassaemia major, hence a systematic review of this topic will help to inform future policy and clinical decision-making about the effectiveness of this intervention.

This Cochrane Review is an update of a previously published version (Jagannath 2011; Jagannath 2014) and complements the existing review on hematopoietic stem cell transplantation for people with sickle cell disease (Oringanje 2016).

OBJECTIVES

To evaluate the effectiveness and safety of different types of allogeneic stem cell transplantation in people with severe transfusion-dependant β -thalassaemia major or β 0/+ thalassaemia variants requiring chronic blood transfusion.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised trials.

Types of participants

People with a documented diagnosis of severe (transfusion-dependent) homozygous β 0/+ thalassaemia or severe variants of β 0/+ thalassaemia requiring chronic blood transfusion and iron chelation therapies.

Types of interventions

Any type of HSCT, including bone marrow (bone marrow transplantation (BMT)), peripheral blood (peripheral blood cell transplantation (PBCT)), or umbilical cord blood (umbilical cord blood transplantation (UCBT)). Wherein the donor could be an HLA-identical related donor; HLA-matched unrelated donor; or with permissible levels of HLA-mismatch donor (Petersdorf 2004) with any type of conditioning regimen for myeloablation and immunosuppression.

Studies comparing these interventions with each other or with standard therapy (regular transfusion and chelation regimen) were eligible for inclusion.

Types of outcome measures

Primary outcomes

1. Event-free survival (event is defined as either β -thalassaemia manifestations or adverse effects of the transplant procedure like graft failure, grade III/IV acute GVHD, or both) the interval from time of randomisation or study entry to the first recurrence of event or to death of any cause. Time periods to be reported on: six months; one year; three years; five years; ten years.
2. Proportion of participants of different levels of overall response (clinical or laboratory): complete (requiring no further treatment); partial (requiring some additional treatment); no response (requiring the same previous baseline treatment). Time periods to be reported on: six months; one year; two years.
3. Quality of life (assessed by validated instruments and scales). Time periods to be reported on: six months; one year; three years; five years; ten years.

Secondary outcomes

1. Time to donor hematological reconstitution (engraftment and full hematological recovery), i.e. post-HSCT absolute neutrophil count greater than 500 for three consecutive days, platelet count higher than 50,000 for one week without transfusion.
2. Number of individuals with stable mixed chimerism (defined as more than 50% donor chimerism by day 180).
3. Incidence of acute and chronic GVHD*.
4. Incidence of graft rejection with recurrence or persistence of β -thalassaemia*.
5. Incidence of other disease or treatment-related morbidities (both conventional and transplant related)*.

*Time periods to be reported on: 30 days, 60 days, 100 days, three months, 12 months.

Search methods for identification of studies

Although there were no language restrictions on included studies we did not retrieve any relevant non-English papers. We will not apply any language restrictions on any studies identified for future updates of the review and will arrange to translate any studies not in the English language.

Electronic searches

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: thalassaemia AND (stem cell* OR bone marrow* OR gene therapy).

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease

Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the [Cochrane Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of last search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register: 18 August 2016.

Searching other resources

We did not identify any relevant studies and were therefore unable to do any searching of the reference lists of relevant articles.

Data collection and analysis

Although no studies were identified for inclusion in this review the following methods of selection of studies, data extraction, assessment of risk of bias and data management will apply for subsequent updates, and when future studies are identified.

Selection of studies

Two review authors (ZF and VJ) will independently assess the abstracts of studies identified from the searches. They will obtain full copies of all relevant and potentially relevant studies (those appearing to meet the inclusion criteria) and those for which there were insufficient data in the title and abstract to make a clear decision. The two review authors will independently assess the full text papers and resolve any disagreement on the eligibility of included studies through discussion and consensus, or through a third author (AH). All irrelevant records will be excluded and the reasons for their exclusion noted in the '[Characteristics of excluded studies](#)' table in the review.

Data extraction and management

Two review authors (ZF and VJ) will independently collect study details and outcome data using a pre-determined form designed for this purpose and enter the study details into the '[Characteristics of included studies](#)' table in the review.

We will extract the following details:

1. study methods: method of allocation; masking of participants, trial investigators and outcome assessors; exclusion of participants after randomisation; and proportion and reasons for losses at follow-up;
2. participants: country of origin; location (private clinic or academic institute); sample size; age; sex; inclusion and exclusion criteria;
3. intervention: type; length of time in follow-up;
4. comparison: type; length of time in follow-up;
5. outcomes as specified in the '[Types of outcome measures](#)' section of this review. Clinically appropriate time points have been selected for the individual outcomes, however, if data are available at other time periods as well, we will state this and we may also consider these. The outcomes not mentioned in our protocol but measured (at any time points) in the studies will also be noted;
6. if any data (stated as being measured at various time points, e.g. within the methods sections of included papers) are not reported, we will contact the trial investigators in an effort to obtain these.

If stated, the authors will record the sources of funding of any included studies.

This information will be used to help assess clinical heterogeneity and the generalisability of any included studies.

Assessment of risk of bias in included studies

Two authors will independently assess the selected studies using a simple contingency form following the domain-based evaluation described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1 ([Higgins 2011a](#)). The authors will compare evaluations, discuss and resolve any disagreements.

The authors will assess the following domains as having either a low, unclear or high risk of bias:

1. sequence generation;
2. allocation concealment;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data;
5. selective outcome reporting.

The authors will report on each of these assessments for each individual study in the '[Assessment of risk of bias in included studies](#)' table.

The authors will categorize the risk of bias in any included studies according to the following:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met;
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were assessed as unclear; or
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

Measures of treatment effect

We will calculate risk ratios (RR) and their associated 95% confidence intervals (CIs) for all dichotomous outcomes. For continuous outcomes the mean relative change from baseline or the mean post-intervention value as well as the difference in means between treatment groups, or by combining the baseline and post-intervention data, and their 95% CIs will be reported. For time-to-event outcomes we will calculate the odds ratio (OR) or hazards ratio (HR) and their 95% CIs using RevMan ([RevMan 2011](#)). The OR will be derived using Peto's method applied to dichotomous data; the HR is derived using a log rank approach or log HRs using the generic inverse-variance method depending on whether data is extracted from the primary studies or obtained from re-analysis of individual patient data.

Unit of analysis issues

Studies with a parallel group design will be included, so participants need to have been randomised to either intervention or control with subsequent analysis at individual allocation level.

Outcomes related only to HSCT and not relevant to conventional treatment, such as event-free survival, graft rejection and graft-related morbidities, are not applicable in studies comparing HSCT with conventional treatment.

Dealing with missing data

We will attempt to retrieve missing data from the investigators in any of the included studies; if we are unsuccessful or if the discrepancies are significant, we will provide a narrative synthesis of the data as reported.

Assessment of heterogeneity

We will assess clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions and the outcomes as specified in the criteria for included studies. Statistical heterogeneity will be assessed using a χ^2 test and the I^2 statistic, where I^2 values of 30% to 60% indicate moderate to high heterogeneity, 50% to 90% substantial heterogeneity and 75% to 100% considerable heterogeneity. We will consider heterogeneity to be significant when the P value are less than 0.10 (Higgins 2003).

Assessment of reporting biases

If we identify sufficient numbers of studies for inclusion in this review, we will assess publication bias according to the recommendations on testing for funnel plot asymmetry (Egger 1997) as described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1 (Higgins 2011b). If we identify asymmetry, we will try to assess other possible causes and explore these in the discussion, if appropriate.

Data synthesis

We will seek statistical support from the Cystic Fibrosis and Genetic Disorders Group. Any data which is reported in the included studies and is relevant to the primary and secondary outcomes of this review will be analysed by two review authors (VJ, AH) using RevMan 5.1 (RevMan 2011) and reported as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1 (Deeks 2011).

Pooling of data to provide estimates of the effects of the interventions will only be undertaken if the included studies have similar interventions received by similar participants. In general, we will use the fixed-effect model; but if there is substantial clinical diversity between the included studies, we will use the random-effects model with studies grouped by mode of action of the intervention. In the event that there are insufficient clinically homogeneous studies for any specific intervention or insufficient study data that can be pooled, we will present a narrative synthesis. In addition, if there is substantial statistical heterogeneity (over 50%) we plan to use the random-effects model.

Subgroup analysis and investigation of heterogeneity

If we include 10 or more studies, and if we identify moderate, substantial or considerable heterogeneity (as defined above) we plan to undertake the following subgroup analyses:

1. Lucarelli staging system: Stage 1, 2, 3 and adult (Appendix 1);
2. age of participant before transplantation under 16 years and 16 years and over;
3. duration of conventional treatment before transplantation (less than five years, five to 10 years and more than 10 years);
4. myeloablative regimen (if studies with different regimens are included);

5. method of stem cell transplant and the HLA matching status of donor (if studies with stem cells from different sources are included).

Sensitivity analysis

We plan to conduct sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments, exclusion of studies with:

- unclear or high risk of bias regarding allocation concealment;
- unclear or high risk of bias regarding blinding of outcomes assessment; and
- unclear or high risk of bias regarding completeness of follow-up;
- cluster-randomised RCTs.

RESULTS

Description of studies

Results of the search

The electronic searches retrieved references to nine studies. After examination of the titles and abstracts of these all but three were eliminated and excluded from further review. Full text copies of these were obtained and were assessed independently by two authors and any disagreement on their eligibility for this review was resolved through discussion and consensus.

Included studies

We retrieved a number of studies in our comprehensive search of the literature but none were eligible and therefore no studies were included in this review.

Excluded studies

We excluded four studies which did not match our inclusion criteria and noted the reasons for their exclusion in the *Characteristics of excluded studies* table (Chandy 2005; Dennison 2003; Gaziev 1995; Irfan 2008).

Risk of bias in included studies

No studies were included in this review.

Effects of interventions

None of the studies retrieved in our searches met our inclusion criteria and therefore no data were available for analysis.

DISCUSSION

The comprehensive search used in this review identified no eligible studies, and thus no robust evidence to support or refute the effectiveness of different types of stem cell transplantation for people with β -thalassaemia major.

Over the last few years there have been a number of studies which have investigated the effectiveness of stem cell transplantation in people with β -thalassaemia. Hematopoietic stem cell transplantation (HSCT) treatment for thalassemia has substantially improved over the last two decades, with advancements in strategies to control transplant-related complications, and preparative regimens. These studies have provided limited data regarding efficacy and safety of stem cell transplantation.

Unfortunately there have been no controlled trials that randomised the participants to stem cell transplantation versus other interventions. The studies that are available either compared different conditioning regimens in stem cell transplantation (Chandy 2005; Dennison 2003; Li 2012) or different risk groups (Hussein 2013). Some non-randomised controlled trials evaluated the outcomes with different donor sources of allogeneic HSCT and different regimens of myeloablative treatments and have indicated the possibility of positive outcomes with HLA matched or related donors over unrelated donors (Andreani 2011; Galambrun 2013; Ghavamzadeh 2013; Hladun 2013; Hongeng 2006; La Nasa 2005; Sodani 2011). Gene therapy for haemoglobinopathies is being developed and may be a curative option in future. However, the questions related to the safety and efficacy of different types of stem cell transplantation remain unanswered.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently limited evidence to either support or refute the effectiveness and safety of different types of stem cell transplantation in people with severe transfusion-dependant β -thalassaemia major or $\beta 0/+$ -thalassaemia variants requiring chronic blood transfusion. The currently available literature on the effectiveness, or otherwise, of these interventions comprises of prospective studies and retrospective conventional therapy trials. Available evidence regarding different conditioning regimens and types of donor cells is progressively changing practice. Current clinical practice will, out of necessity, continue to be based on this evidence in addition to both a physician's clinical experience and the individual circumstances and preferences of well-informed patients. The therapy should be individualised taking into consideration age, clinical status, willingness as well as capability and compliance to adhere to the appropriate transfusion-chelation regimen and according to availability of resources. A risk class stratification based approach to transplantation in thalassaemia based on these factors is used to prognosticate outcome. The decision making will also have to consider other essential factors such as the availability of suitable donors, class of HSCT-eligibility based on optimal conventional therapy, and the risk of regimen-related side effects such as early death or late effects, i.e. chronic graft versus host disease (GVHD), sterility and cancer.

Clinicians are recommended to follow the current practice recommendation of human leucocyte antigen (HLA) typing all individuals with thalassaemia, together with their parents and siblings and when an HLA donor is available, HSCT is highly recommended in people with class 1 and 2 thalassaemia, as well as for those of class 3 who are aged less than 17 years old and those without matched family or unrelated donors could benefit from haploidentical mother-to-child transplantation (Isgro 2010; Lucarelli 2012).

Thus, the decision to treat should include a full risk assessment of the potential harms and benefits of withholding stem cell transplantation, while balancing the possible sequelae of chronic transfusion and chelation therapy against the risk of potential adverse events.

Implications for research

Although they may appear to be warranted, it is not clear whether further studies are feasible for this intervention and some of the comparisons, especially as HSCT has become more widely accepted as a mode of curative intervention for β -thalassaemia, albeit not based on evidence from RCTs. Scientific advances for this intervention are focused on trials examining alternative conditioning regimens, alternative sources of stem cells and alternative donors (Jacobsohn 2004). It may be valuable to carry out a subgroup analysis across some of these studies to identify the optimal myeloablative regimen donor type and stem cell source.

The randomised controlled trial still remains the best study design to answer these questions and these trials should be performed in homogeneous study populations (for example, regarding stage of disease and individual age) and have a long-term follow up. Different risk groups should be taken into account. Future updates of reviewing the ongoing trials examining alternative conditioning regimens, alternative sources of stem cells and alternative donors can provide conclusions regarding the best treatment strategy.

ACKNOWLEDGEMENTS

The authors would like to thank the Cochrane Cystic Fibrosis and Genetic Disorders Group for their support throughout the development of this review. We would also like to thank Nianfang Hu (NH) for her contribution to the original review (Jagannath 2011).

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Chandy 2005	Randomisation to conditioning regimen prior to BMT.
Dennison 2003	Randomisation to conditioning regimen prior to BMT.
Gaziev 1995	Randomisation to conditioning regimen prior to BMT.
Irfan 2008	Not a prospective study.

BMT: bone marrow transplantation

APPENDICES

Appendix 1. Lucarelli staging

1	absence of hepatomegaly (enlarged liver), regular iron chelation before transplant, absence of fibrosis in pretransplant liver biopsy result
2	hepatomegaly, a history of irregular iron chelation before transplant, histological evidence of liver fibrosis, or various combinations of the above
3	all of the following: large liver, poor compliance with chelation therapy, liver damage
4	class 2 or 3, irregular iron chelation, with a range of clinical symptoms and other diagnoses

Appendix 2. Glossary

Term	Meaning
ablate	to remove or otherwise destroy the biological function of any part (e.g. bone marrow)
alkylating agent	agents used in cancer treatment that attaches an alkyl group (C_nH_{2n+1}) (hydrocarbon) to DNA (molecule of cell nucleus)
allogeneic	denoting or relating to cells or tissues from individuals belonging to the same species but genetically dissimilar (and hence immunologically incompatible)
antithymocyte globulin	an infusion of horse or rabbit-derived antibodies against human T cells which is used in the prevention and treatment of acute rejection in organ transplantation
chromatography	the collective term for a set of laboratory techniques for the separation of mixtures
electrophoresis	the motion of dispersed particles relative to a fluid under the influence of a spatially uniform electric field
endogenous	caused by factors inside the organism or system
erythropoiesis	the process by which red blood cells (erythrocytes) are produced
gonadal failure	the condition in which the production of sex hormones and germ cells are inadequate
haemolytic anaemia	anaemia due to the abnormal breakdown of red blood cells
haemosiderosis	a form of iron overload disorder resulting in the accumulation of haemosiderin which is an iron-storage complex
hepcidin	a peptide hormone produced by the liver which is involved in the master regulation of iron homeostasis in humans and other mammals
intramedullary	a medical term meaning the inside of a bone
iron chelation	the process by which some molecules called chelator bind to iron and remove them as well as neutralise the toxic property (desferrioxamine)
myeloablation	the depletion of the bone marrow cells by the administration of high doses of chemotherapy or radiation therapy
portal bridging	a form of confluent necrosis between some areas of liver in chronic liver disease
purine analogue	anti-metabolites which mimic the structure of metabolic purines (molecules in the cell nucleus)

WHAT'S NEW

Date	Event	Description
17 November 2016	New citation required but conclusions have not changed	Minor edits have been made throughout the review.

Date	Event	Description
17 November 2016	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Haemoglobinopathies Trials Register identified nine potentially relevant references. Eight were discarded and one was added to the 'Excluded studies' section of the review (Irfan 2008).

HISTORY

Protocol first published: Issue 9, 2010

Review first published: Issue 10, 2011

Date	Event	Description
13 April 2015	Amended	Contact details updated.
17 February 2014	New citation required but conclusions have not changed	Minor changes have been made throughout the text of this updated review.
17 February 2014	New search has been performed	A new search of the Cochrane Cystic Fibrosis and Genetic Disorders Haemoglobinopathies Trials Register did not identify any potentially eligible trials for inclusion in the review.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
<i>Protocol stage:</i> draft the protocol	ZF/AH/VJ/NH/AS
<i>Review stage:</i> select which studies to include (2 + 1 arbiter)	ZF/AH/VJ
<i>Review stage:</i> extract data from studies (2 people)	ZF/AH/VJ
<i>Review stage:</i> enter data into RevMan	ZF/AH/VJ
<i>Review stage:</i> carry out the analysis	ZF/AH/VJ
<i>Review stage:</i> interpret the analysis	ZF/AH/VJ/NH/AS
<i>Review stage:</i> draft the final review	ZF/AH/VJ/NH/AS
<i>Update stage:</i> update the review	ZF/AH/VJ/AS

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol stated gene therapy as an intervention to be included in this review; a *post hoc* change has excluded gene therapy since the mode of action and logistics concerning the intervention are different and hence this should be considered in a separate review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hematopoietic Stem Cell Transplantation; beta-Thalassemia [*therapy]

MeSH check words

Humans