Cochrane Library

Cochrane Database of Systematic Reviews

Hematopoietic stem cell transplantation for people with β-thalassaemia (Review)

Sharma A, Jagannath VA, Puri L

Sharma A, Jagannath VA, Puri L.
Hematopoietic stem cell transplantation for people with β-thalassaemia.
Cochrane Database of Systematic Reviews 2021, Issue 4. Art. No.: CD008708.
DOI: 10.1002/14651858.CD008708.pub5.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Hematopoietic stem cell transplantation for people with β-thalassaemia

Akshay Sharma[1], Vanitha A Jagannath[2], Latika Puri[3]

[1]Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, Tennessee, USA. [2]Department of Paediatrics, American Mission Hospital, Manama, Bahrain. [3]St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA

Contact: Akshay Sharma, mail@akshaysharma.in, akshay.sharma@stjude.org.

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 4, 2021.

Citation: Sharma A, Jagannath VA, Puri L. Hematopoietic stem cell transplantation for people with β-thalassaemia. *Cochrane Database of Systematic Reviews* 2021, Issue 4. Art. No.: CD008708. DOI: 10.1002/14651858.CD008708.pub5.

ABSTRACT

Background

Thalassaemia is an autosomal recessive blood disorder, caused by mutations in globin genes or their regulatory regions, resulting in a reduced rate of synthesis of one of the globin chains that make up haemoglobin. In β-thalassaemia 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 increased destruction (haemolysis) and ineffective erythropoiesis. The conventional treatment is based on the correction of haemoglobin through regular red blood cell transfusions and treating the iron overload that develops subsequently with iron chelation therapy. Although, early detection and initiations of such supportive treatment has improved the quality of life for people with transfusion-dependent thalassaemia, allogeneic hematopoietic stem cell transplantation is the only widely available therapy with a curative potential. Gene therapy for β-thalassaemia has recently received conditional authorisation for marketing in Europe, and may soon become widely available as another alternative therapy with curative potential for people with transfusion-dependent thalassaemia. This is an update of a previously published Cochrane Review.

Objectives

To evaluate the effectiveness and safety of different types of hematopoietic stem cell transplantation, in people with transfusion-dependent β-thalassaemia.

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. We also searched online trial registries.

Date of the most recent search: 07 April 2021.

Selection criteria

Randomised controlled trials and quasi-randomised controlled trials comparing 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 trials and had planned to extract data and assess risk of bias using standard Cochrane methodologies and assess the quality using GRADE approach, but no trials were identified for inclusion in the current review.

Main results

No relevant trials 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 hematopoietic stem cell transplantation in people with transfusion-dependent β-thalassaemia. 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 transfusion-dependent β-thalassaemia

Review question

We reviewed whether different types of stem cell transplantation are safe and effective in people with transfusion-dependent β-thalassaemia.

Background

Thalassaemia is a disorder that occurs because of a mutation in either the α- or β-globin genes causing decreased production of haemoglobin (a protein found in red blood cells that carries oxygen) and increased destruction of red blood cells. Decreased production of haemoglobin and destruction of red blood cells leads to anaemia and significant morbidity in affected individuals. While anaemia can be treated effectively with regular blood transfusions, repeated transfusions lead to the accumulation of iron in the body, which unless treated with iron chelation can result in multiorgan disease particularly heart and lung. These toxicities tend to accumulate over time leading to reduced quality of life and early death. Additionally, blood transfusions do 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 either a healthy donor (allogeneic hematopoietic stem cell transplantation) or genetically correcting the recipient's own cells and reinfusing them back into the individual (autologous gene therapy). These stem cells then produce normal red blood cells containing normal amounts of globin chains and thus ameliorate anaemia.

Search date

The evidence is current to: 07 April 2021.

Key results

The review authors did not find any randomised controlled trials assessing the effectiveness and safety of different types of hematopoietic stem cell transplantation in people with transfusion-dependent β-thalassaemia.

BACKGROUND

Description of the condition

Please refer to an appendix for a glossary of terms (Appendix 1).

Thalassaemia is an autosomal recessive disorder caused by mutations in either the α- or β-globin genes or their regulatory elements, resulting in a quantitative defect in haemoglobin production. In β-thalassaemia there is an inadequate production of β-globin chains, while in α-thalassaemia there is an inadequate production of α-globin chains. In β-thalassaemia, decreased production of β-globin chains results in decreased haemoglobin production and anaemia. Additionally there is an imbalance in the amounts of α- and β-globin chains with accumulation of excess α-globin tetramers that precipitate in erythroid precursors, cause oxidative damage and result in extensive destruction of RBC precursors (ineffective erythropoiesis) (Weatherall 2002).

Previously, thalassaemia was classified into thalassaemia major, thalassaemia intermedia and thalassaemia minor depending upon disease severity. Those with thalassaemia minor are usually asymptomatic or may have a very mild microcytic anaemia. Thalassaemia major on the other hand usually results in severe anaemia requiring lifelong blood transfusion therapy and aggressive medical management. People with thalassaemia intermedia have a clinical presentation in between these two extremes with varying clinical severity from mild, moderate to severe anaemia requiring no, intermittent to chronic transfusions respectively. The clinical classification of thalassaemias has since evolved and currently individuals with thalassaemia are classified into either transfusion-dependent thalassaemia (TDT) or non-transfusion-dependent thalassaemia (NTDT) (Cappellini 2014; Taher 2013).

The prevalence of β-thalassaemia ranges from 1% to 20% in regions across Africa, the Mediterranean, Middle East, the Indian subcontinent, and Southeast Asia (Weatherall 2001). Approximately 150 million people worldwide carry mutations in β-globin genes (Modell 2008) and over two million people with β-thalassaemia major require blood transfusions globally (Weatherall 2002). While β-thalassaemia is the clinically more significant form, α-thalassaemia is probably more prevalent in the tropical and sub-tropical areas with an estimated 5% of the world population having an α-thalassaemia gene variant (Piel 2014). The actual number of people suffering from thalassaemia is unknown in low- and middle-income countries, where genetic screening resources are often very limited.

Children with thalassaemia usually become symptomatic within the first year of life with symptoms of severe anaemia, jaundice, irritability, feeding problems, and failure to thrive. If they remain untreated they may develop bone marrow expansion, pathological fractures, skeletal deformities and extramedullary masses (Rachmilewitz 2011). Mainstay of treatment for transfusion-dependent thalassaemia is chronic blood transfusions and iron chelation therapy. Frequent transfusions cause iron overload which results in complications like hepatitis, liver fibrosis and cardiomyopathy, necessitating iron chelation therapy (Dogramaci 2009; Olivieri 1999; Weatherall 2002). Safe routine blood transfusions and chelation therapy along with improvement in supportive care have significantly improved the survival rates and quality of life of people with transfusion-dependent thalassaemia, particularly in high-income countries (Borgna-Pignatti 2004). However, thalassaemia remains a significant cause of childhood mortality in countries where access to regular and safe transfusions and regular chelation therapy remains challenging.

Description of the intervention

Hematopoietic stem cell transplantation (HSCT) replaces the ineffective endogenous erythropoiesis, corrects the underlying anaemia and offers a curative therapy. The best outcomes after HSCT for transfusion-dependent thalassaemia have been using bone marrow derived hematopoietic stem cells from a human leukocyte antigen (HLA) matched sibling donor (Angelucci 2014; Locatelli 2013; Hussein 2013; Di Bartolomeo 2008). Use of alternative sources of hematopoietic stem cells including umbilical cord blood and peripheral blood stem cells have also been investigated in recent years (Locatelli 2013; Schrier 2005). If an HLA-identical related donor is not available, an HLA-matched unrelated donor may also be used for HSCT (Petersdorf 2004).

Adverse events associated with the HSCT include risk of graft failure or rejection, life-threatening infections and graft versus host disease (GVHD). Long-term morbidities associated with the procedure include secondary malignancies, infertility, gonadal failure, psychological disturbances and employment-related problems (Di Bartolomeo 2008). Reduced intensity conditioning regimens may be used to decrease transplant related morbidity but unfavourable outcomes, such as graft rejection, are more likely with reduced intensity conditioning regimens (Iannone 2003; Jacobsohn 2004; van Besien 2000).

The use of autologous genetically-modified stem cells carrying a normal β-globin gene, i.e. gene therapy, has emerged as an attractive potential treatment option for people with β-thalassaemia (Sadelain 2005). This approach avoids the immune complications associated with an allogeneic donor as well as issues of donor availability. After the initial success of early phase clinical trials, a type of gene therapy for β-thalassaemia has recently received conditional authorisation for marketing in Europe (EMA Zynteglo 2019).

How the intervention might work

Hematopoietic stem cell transplantation replaces ineffective erythropoiesis with an effective allogeneic substitute. The transplanted hematopoietic progenitor cells take over the function and produce normal red blood cells (RBC). This process subsequently corrects the anaemia and eliminates the haemolytic process. This ameliorates the life long need for transfusions and chelation therapy.

Why it is important to do this review

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

The first stem cell transplant that successfully cured β-thalassaemia was performed in 1982 (Thomas 1982) and since then a number of treatment 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 transfusion-dependent β-thalassaemia, 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; Jagannath 2016) and complements the existing review on hematopoietic stem cell transplantation for people with sickle cell disease (Oringanje 2020).

OBJECTIVES

To evaluate the effectiveness and safety of different types of stem cell transplantation in people with transfusion-dependent thalassaemia.

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 diagnosis of transfusion-dependent thalassaemia.

Types of interventions

Any type of HSCT, including bone marrow (bone marrow), peripheral blood (peripheral blood derived stem cells), or umbilical cord blood; any donor (an HLA-identical related donor, HLA-matched unrelated donor, or an HLA -mismatched donor) with any type of conditioning regimen will be included. We will also include trials that have autologous HSCT with genetically modified hematopoietic stem cells (gene therapy) as one of the interventions.

Trials 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, need for resumption of blood transfusions, or adverse effects of the transplant procedure like graft failure, grade III/IV acute GVHD, or chronic GVHD) the interval from time of randomisation or trial entry to the first occurrence of event or to death of any cause.
2. Quality of life (assessed by validated instruments and scales).

Secondary outcomes

1. Time to engraftment, i.e. post-HSCT absolute neutrophil count greater than 500/microlitre for three consecutive days, platelet count higher than 50,000/microlitre 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.

Search methods for identification of studies

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

Electronic searches

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Group's Haemoglobinopathies Trials Register using the terms: (thalassaemia OR (haemoglobinopathies AND general)) 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 (Clinical Trials) (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 Public Health Agency Annual Scientific Meeting (formerly the Caribbean Health Research Council Meeting); 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's website.

We searched the following clinical trials registries: ClinicalTrials.gov; and the WHO ICTRP. For the full search strategies, please refer to the relevant appendix (Appendix 2). Date of the most recent search: 20 April 2020.

Date of last search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register: 07 April 2021.

Searching other resources

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

Data collection and analysis

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

Selection of studies

Two review authors will independently assess the abstracts of trials identified from the searches. We will obtain full copies of all relevant and potentially-relevant trials (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 trials through discussion and consensus, or through consultation with a member of the editorial team at the Cochrane Cystic Fibrosis and Genetic Disorders Group or a third author. We will exclude all irrelevant records and note the reasons for their exclusion in the 'Characteristics of excluded studies' table in the review.

Data extraction and management

Two review authors will independently collect trial details and outcome data using a pre-determined form designed for this purpose and enter the trial details into the 'Characteristics of included studies' table in the review.

We will extract the following details:

1. trial 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; 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 trials 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 reported, the authors will record the sources of funding of any included trials.

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

Assessment of risk of bias in included studies

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

We 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.

We will report on each of these assessments for each individual trial in the 'Assessment of risk of bias in included studies' table.

We will categorize the risk of bias in any included trials 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, we will report 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. For time-to-event outcomes, we will calculate the odds ratio (OR) or hazards ratio (HR) and their 95% CIs using RevMan (RevMan 2011). For dichotomous data, we will derive the OR using Peto's method; we will derive the HR using a log rank approach or log HRs using the generic inverse-variance method depending on whether data are extracted from the primary trials or obtained from re-analysis of individual patient data.

Unit of analysis issues

We will include trials with a parallel group design, therefore, 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 trials comparing HSCT with conventional treatment.

Dealing with missing data

We will attempt to retrieve missing data from the investigators in any of the included trials; 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 trials, the similarity between the types of participants, the interventions and the outcomes as specified in the criteria for included trials. We will assess statistical heterogeneity using a Chi^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 trials 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* (Sterne 2011). 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. Review authors will analyse any data which are reported in the included trials and are relevant to the primary and secondary outcomes of this review using RevMan 5.1 (RevMan 2011) and report these as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions 5.1* (Deeks 2011).

We will only undertake the pooling of data to provide estimates of the effects of the interventions if the included trials 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 trials, we will use the random-effects model with trials grouped by mode of action of the intervention. In the event that there are insufficient clinically homogeneous trials for any specific intervention or insufficient trial 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 trials, 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 3);
2. age of participant before transplantation under 10 years and 10 years and over;
3. myeloablative regimen (if trials with different regimens are included);
4. method of stem cell transplant and the HLA matching status of donor (if trials 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 trials 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.

Summary of findings and assessment of the certainty of the evidence

In a post hoc change, we aim, in future versions of the review, to use the GRADE approach to create a 'Summary of findings' table, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We will determine the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results or high probability of publication bias. We will downgrade evidence by one level if we consider the limitation to be serious and by two levels if very serious.

We aim to present the following outcomes within a summary of findings table for each intervention comparison:

- event-free survival;
- proportion of participants experiencing different levels of overall response;
- quality of life.

RESULTS

Description of studies

Results of the search

The electronic searches retrieved references to several studies. After examination of the titles and abstracts of these all but four 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

Summary of main results

A comprehensive search used in this review identified no eligible randomised controlled trials to support or refute the effectiveness of different types of stem cell transplantation for people with transfusion-dependent thalassaemia in comparison to standard supportive care therapy. However, no trials were eligible for inclusion in the review.

Overall completeness and applicability of evidence

No trials were eligible for inclusion in the review.

Quality of the evidence

No trials were eligible for inclusion in the review.

Potential biases in the review process

We are unaware of any biases in the review process.

Agreements and disagreements with other studies or reviews

Since the curative potential of HSCT for thalassaemia was first established, more than 4000 transplant procedures have been reported worldwide (Shenoy 2017). Outcomes after transplant for transfusion-dependent thalassaemia have substantially improved over the last two decades with advancements in strategies to control transplant-related complications, and reduction in toxicity associated with preparative regimens. Studies have shown that

early HSCT before the accumulation of thalassaemia related organ dysfunction is associated with reduced transplant related toxicity. When HSCT is performed utilizing HLA matched sibling donor before 14 years of age, transplant related mortality is less than 10% and if performed before five years of age, transplant related mortality is further reduced to less than 5% (Baronciani 2016). However, most of these data are based on case series and observational cohort studies. Various reports have either compared different conditioning regimens for HSCT (Chandy 2005; Dennison 2003; Li 2012) or different risk groups (Hussein 2013) in a non-randomised fashion. Non-randomised studies have also evaluated outcomes with different donor sources and conditioning regimens, and have indicated better 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). A recent case control study noted that the overall survival for both paediatric and adult patients with thalassaemia was similar with either HSCT or chronic transfusion therapy (Caocci 2017). However, HSCT is associated with improved health related quality of life measures compared with chronic transfusion therapy (Cheuk 2008; Caocci 2011; La Nasa 2013). While the cost of treatment may vary between countries, the estimated costs of an allogeneic HSCT from a sibling are almost invariably lower than the cumulative cost of conventional therapy with lifelong blood transfusion and iron chelation therapy (Weidlich 2016; Sruamsiri 2013). A recent analysis similarly found that while autologous gene therapy for thalassaemia is likely to be costlier than allogeneic HSCT, it would be associated with fewer long term complications than allogeneic HSCT, and hence in the end more cost effective than either allogeneic HSCT or conventional therapy (Coquerelle 2019). Given the emerging body of evidence regarding the potential benefit of HSCT and gene therapy to cure thalassaemia, there may not be a possibility for a randomised clinical trial comparing standard transfusion therapy to allogeneic HSCT or gene therapy. Further, it may be ethically challenging to recruit patients to such a clinical trial especially since now HSCT is known to be effective from several cohort studies. Nevertheless, randomised studies may still be conducted to compare relative safety and efficacy of various donor sources and supportive care practices.

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 transfusion-dependent thalassaemia. The currently available literature on the effectiveness, or otherwise, of these interventions comprises of cohort studies or non-randomised clinical trials. Available evidence regarding different conditioning regimens and types of donors and graft sources is a continuously changing practice. Current clinical practice will, out of necessity, continue to be based on the available 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. The decision making will also have to consider other essential factors such as the availability of suitable donors, and the risk of regimen-related side effects such as early death or late effects, sterility and cancer.

Clinicians are recommended to follow the current practice recommendation for HLA typing all individuals with thalassaemia, together with their parents and siblings. When a human leukocyte antigen (HLA) donor is available, hematopoietic stem cell transplantation (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. Those without matched family or unrelated donors could benefit from haploidentical transplantation (Isgro 2010; Lucarelli 2012; Angelucci 2014; Baronciani 2016).

Thus, the decision to treat should include a full risk assessment of the potential risks and benefits of stem cell transplantation compared to those of chronic transfusion and chelation therapy.

Implications for research

As HSCT has become more widely accepted as a mode of curative intervention for thalassaemia, it is not clear whether randomised studies comparing HSCT with alternative therapies are feasible. Scientific reports have focused on trials examining alternative conditioning regimens, 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 conditioning regimen, donor type and stem cell source.

A randomised controlled trial still remains the best study design to answer some of the questions of comparative efficacy and safety. These trials should be performed in homogeneous study populations and have a long-term follow up. Future updates reviewing the ongoing trials examining alternative conditioning regimens, sources of stem cells and 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), Amani Al Hajeri (AH) and Zbys Fedorowicz (ZF) for their contributions to the previous versions of this review (Jagannath 2011).

REFERENCES

References to studies excluded from this review

Chandy 2005 *{published data only}*

Chandy M, Balasubramanian P, Ramachandran SV, Mathews V, George B, Dennison D, et al. Randomized trial of two different conditioning regimens for bone marrow transplantation in thalassemia--the role of busulfan pharmacokinetics in determining outcome. *Bone Marrow Transplant* 2005;**36**(10):839-45. [CFGD REGISTER: TH28e] [PMID: 16151422]

Dennison D, Chandy M, Poonkuzhali B, Srivastava A, Shaji RV, Remington NEJ, et al. Plasma busulfan levels influence rejection in bone marrow transplantation for homozygous beta thalassaemia. *Blood* 1998;**92**(10 Suppl 1):127a. [CFGD REGISTER: TH28b]

Poonkuzhali B, Chandy M, Srivastava A, Dennison D, Kanagasabapathy AS, Krishnamoorthy R. Correlation of hepatic glutathione S-transferase levels with busulfan pharmacokinetics in children with homozygous beta thalassemia undergoing bone marrow transplantation. *Blood* 1998;**92**(10 Suppl 1):128a. [CFGD REGISTER: TH28a]

Poonkuzhali B, Chandy M, Srivastava A, Dennison D, Krishnamoorthy R. Glutathione S-transferase activity influences busulfan pharmacokinetics in patients with beta thalassemia major undergoing bone marrow transplantation. *Drug Metabolism and Disposition* 2001;**29**(3):264-7. [CENTRAL: CN-01731482] [CFGD REGISTER: TH28f] [EMBASE: 32179525] [PMID: 11181493]

Poonkuzhali B, Srivastava A, Quernin MH, Dennison D, Aigrain EJ, Kanagasabapathy AS, et al. Pharmacokinetics of oral busulphan in children with beta thalassaemia major undergoing allogeneic bone marrow transplantation. *Bone Marrow Transplantation* 1999;**24**(1):5-11. [CFGD REGISTER: TH28c]

Srivastava A, Poonkuzhali B, Shaji RV, George B, Mathews V, Chandy M, et al. Glutathione S-transferase M1 polymorphism: a risk factor for hepatic venoocclusive disease in bone marrow transplantation. *Blood* 2004;**104**(5):1574-7. [CFGD REGISTER: TH28d]

Dennison 2003 *{published data only}*

Dennison JD, Quernin MH, Al Kindi S, Muralitharan S, Tauro M, Kanan K, et al. Oral versus intravenous busulfan in bone marrow transplantation for thalassemia. *Blood* 2003;**102**(11). [ABSTRACT NO.: 5581] [ABSTRACT NO.: 5581] [CFGD REGISTER: TH48]

Gaziev 1995 *{published data only}*

Gaziev D, Giardini C, Angelucci E, Polchi P, Galimberti M, Baronciani D, et al. Intravenous chelation therapy during transplantation for thalassemia. *Haematologica* 1995;**80**(4):300-4. [CFGD REGISTER: TH10] [PMID: 7590497]

Irfan 2008 *{published data only}*

Irfan M, Hashmi K, Adil S, Shamsi T, Farzana T, Ansari S, et al. Beta-thalassaemia major: bone marrow versus peripheral blood stem cell transplantation. *Journal of the Pakistan Medical Association* 2008;**58**(3):107-10. [CFGD REGISTER: TH157] [PMID: 18517111]

Additional references

Andreani 2011

Andreani M, Testi M, Battarra M, Lucarelli G. Split chimerism between nucleated and red blood cells after bone marrow transplantation for haemoglobinopathies. *Chimerism* 2011;**2**(1):21-2. [PMID: 21547033]

Angelucci 2014

Angelucci E, Matthes-Martin S, Baronciani D, Bernaudin F, Bonanomi S, Cappellini MD, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. *Haematologica* 2014;**99**(5):811-20. [PMID: 24790059]

Baronciani 2016

Baronciani D, Angelucci E, Potschger U, Gaziev J, Yesilipek A, Zecca M, et al. Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000-2010. *Bone Marrow Transplant* 2016;**51**(4):536-41. [PMID: 26752139]

Borgna-Pignatti 2004

Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, DelVecchio GC, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica* 2004;**89**(10):1187-93. [PMID: 15477202]

Caocci 2011

Caocci G, Efficace F, Ciotti F, Roncarolo MG, Vacca A, Piras E, et al. Prospective assessment of health-related quality of life in pediatric patients with beta-thalassemia following hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2011;**17**(6):861-6. [DOI: 10.1016/j.bbmt.2010.09.011] [PMID: 20870029]

Caocci 2017

Caocci G, Orofino MG, Vacca A, Piroddi A, Piras E, Addari MC, et al. Long-term survival of beta thalassemia major patients treated with hematopoietic stem cell transplantation compared with survival with conventional treatment. *American Journal of Hematology* 2017;**92**(12):1303-10. [DOI: 10.1002/ajh.24898] [PMID: 28850704]

Cappellini 2014

Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 3rd edition. Nicosia, Cyprus: Thalassaemia International Federation, 2014. [ISBN-13: 978-9963-717-06-4]

Cheuk 2008

Cheuk DK, Mok AS, Lee AC, Chiang AK, Ha SY, Lau YL, et al. Quality of life in patients with transfusion-dependent thalassemia after hematopoietic SCT. *Bone Marrow Transplant* 2008;**42**(5):319-27. [DOI: 10.1038/bmt.2008.165] [PMID: 18560410]

Coquerelle 2019

Coquerelle S, Ghardallou M, Rais S, Taupin P, Touzot F, Boquet L, et al. Innovative Curative Treatment of Beta Thalassemia: Cost-Efficacy Analysis of Gene Therapy Versus Allogenic Hematopoietic Stem-Cell Transplantation. *Hum Gene Ther* 2019;**30**(6):753-61. [DOI: 10.1089/hum.2018.178] [PMID: 30700149]

Deeks 2011

Deeks J, Higgins JP, Altman D. Chapter 9 Analysing data and undertaking meta-analysis. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Di Bartolomeo 2008

Di Bartolomeo P, Santarone S, Di Bartolomeo E, Olioso P, Bavaro P, Papalinetti G, et al. Long-term results of survival in patients with thalassemia major treated with bone marrow transplantation. *American Journal of Hematology* 2008;**83**(7):528-30. [PMID: 18383328]

Dogramaci 2009

Dogramaci AC, Savas N, Ozer B, Duran N. Skin diseases in patients with beta-thalassemia major. *International Journal of Dermatology* 2009;**48**(10):1057-61.

Egger 1997

Egger M, Davey-Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629-34.

EMA Zynteglo 2019

European Medicines Agency. Zynteglo. www.ema.europa.eu/en/medicines/human/EPAR/zynteglo (accessed 20 April 2020).

Galambrun 2013

Galambrun C, Pondarre C, Bertrand Y, Loundou A, Bordigoni P, Frange P, et al. French multicenter 22-year experience in stem cell transplantation for beta-thalassemia major: lessons and future directions. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation* 2013;**19**(1):62-8. [PMID: 22892550]

Ghavamzadeh 2013

Ghavamzadeh A, Alimoghaddam K, Ghaffari F, Derakhshandeh R, Jalali A, Jahani M. Twenty years of experience on stem cell transplantation in Iran. *Iranian Red Crescent medical journal* 2013;**15**(2):93-100. [PMID: 23682320]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011

Higgins JP, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Hladun 2013

Hladun R, Elorza I, Olive T, Dapena JL, Llort A, Sanchez de Toledo J, et al. Results of hematopoietic stem cell transplantation in hemoglobinopathies: thalassemia major and sickle cell disease [Resultados del trasplante de progenitores hematopoyeticos en hemoglobinopatias: talasemia maior y enfermedad drepanocitica.]. *Anales de Pediatria* 2013;**79**(2):75-82. [PMID: 23402775]

Hongeng 2006

Hongeng S, Pakakasama S, Chuansumrit A, Sirachainan N, Kitpoka P, Udomsubpayakul U, et al. Outcomes of transplantation with related- and unrelated-donor stem cells in children with severe thalassemia. *Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation* 2006;**12**(6):683-7. [PMID: 16737942]

Hussein 2013

Hussein AA, Al-Zaben A, Ghatasheh L, Natsheh A, Hammada T, Abdel-Rahman F, et al. Risk adopted allogeneic hematopoietic stem cell transplantation using a reduced intensity regimen for children with thalassemia major. *Pediatric Blood & Cancer* 2013;**60**(8):1345-9. [PMID: 23424175]

Iannone 2003

Iannone R, Casella JF, Fuchs EJ, Chen AR, Jones RJ, Woolfrey A, et al. Results of minimally toxic nonmyeloablative transplantation in patients with sickle cell anemia and beta-thalassemia. *Biology of Blood and Marrow Transplantation* 2003;**9**(8):519-28. [PMID: 12931121]

Isgro 2010

Isgro A, Gaziev J, Sodani P, Lucarelli G. Progress in hematopoietic stem cell transplantation as allogeneic cellular gene therapy in thalassemia. *Annals of the New York Academy of Sciences* 2010;**1202**:149-54. [PMID: 20712786]

Jacobsohn 2004

Jacobsohn DA, Duerst R, Tse W, Kletzel M. Reduced intensity haemopoietic stem-cell transplantation for treatment of non-malignant diseases in children. *Lancet* 2004;**364**(9429):156-62. [PMID: 15246728]

La Nasa 2005

La Nasa G, Argiolu F, Giardini C, Pession A, Fagioli F, Caocci G, et al. Unrelated bone marrow transplantation for beta-thalassemia patients: The experience of the Italian Bone Marrow Transplant Group. Annals of the New York Academy of Sciences 2005;**1054**:186-95. [PMID: 16339665]

La Nasa 2013

La Nasa G, Caocci G, Efficace F, Dessì C, Vacca A, Piras E, et al. Long-term health-related quality of life evaluated more than

20 years after hematopoietic stem cell transplantation for thalassemia. *Blood* 2013;**122**(13):2262-70. [PMID: 23958950]

Li 2012

Li C, Wang Y, Wu X, Pei F, He Y, Feng X, et al. [Pretreatment doses of antithymocyte globubin-fresenius for allogeneic hematopoietic stem cell transplantation for beta-thalassemia major]. *Journal of Southern Medical University* 2012;**32**(5):691-4. [PMID: 22588927]

Locatelli 2013

Locatelli F, Kabbara N, Ruggeri A, Ghavamzadeh A, Roberts I, Li CK, et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. *Blood* 2013;**122**(6):1072-8. [PMID: 23692854]

Lucarelli 1999

Lucarelli G, Clift RA, Galimberti M, Angelucci E, Giardini C, Baronciani D, et al. Bone marrow transplantation in adult thalassemic patients. *Blood* 1999;**93**(4):1164-7. [PMID: 9949158]

Lucarelli 2008

Lucarelli G. Advances in the allogeneic transplantation for thalassemia. Blood Reviews 2008;**22**(2):53-63. [PMID: 18039551]

Lucarelli 2012

Lucarelli G, Isgro A, Sodani P, Gaziev J. Hematopoietic stem cell transplantation in thalassemia and sickle cell anemia. *Cold Spring Harbor perspectives in medicine* 2012;**2**(5):a011825. [PMID: 22553502]

Modell 2008

Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bulletin of the World Health Organization* 2008;**86**(6):480-7.

Olivieri 1999

Olivieri NF. The beta-thalassemias. *New England Journal of Medicine* 1999;**341**(2):99-109.

Oringanje 2020

Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No: CD007001. [DOI: 10.1002/14651858.CD007001.pub5] [PMID: 32617981]

Petersdorf 2004

Petersdorf EW. HLA matching in allogeneic stem cell transplantation. *Current Opinion in Hematology* 2004;**11**(6):386-91. [PMID: 15548992]

Piel 2014

Piel FB, Weatherall DJ. The α-thalassemias. *N Engl J Med* 2014;**371**(20):1908-16. [PMID: 25390741]

Rachmilewitz 2011

Rachmilewitz EA, Giardina PJ. How I treat thalassemia. *Blood* 2011;**118**(13):3479-88. [PMID: 21813448]

RevMan 2011 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.1. The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Sadelain 2005

Sadelain M, Lisowski L, Samakoglu S, Rivella S, May C, Riviere I. Progress toward the genetic treatment of the beta-thalassemias. *Annals of the New York Academy of Sciences* 2005;**1054**:78-91. [PMID: 16339654]

Schrier 2005

Schrier SL, Angelucci E. New strategies in the treatment of the thalassemias. *Annual Review of Medicine* 2005;**56**:157-71.

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Shenoy 2017

Shenoy S, Angelucci E, Arnold SD, Baker KS, Bhatia M, Bresters D, et al. Current Results and Future Research Priorities in Late Effects after Hematopoietic Stem Cell Transplantation for Children with Sickle Cell Disease and Thalassemia: A Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant* 2017;**23**(4):552-61. [DOI: 10.1016/j.bbmt.2017.01.009] [PMID: 28065838]

Sodani 2011

Sodani P, Isgro A, Gaziev J, Paciaroni K, Marziali M, Simone MD, et al. T cell-depleted hla-haploidentical stem cell transplantation in thalassemia young patients. *Pediatric Reports* 2011;**3 Suppl 2**:e13. [PMID: 22053275]

Sruamsiri 2013

Sruamsiri R, Chaiyakunapruk N, Pakakasama S, Sirireung S, Sripaiboonkij N, Bunworasate U, et al. Cost utility analysis of reduced intensity hematopoietic stem cell transplantation in adolescence and young adult with severe thalassemia compared to hypertransfusion and iron chelation program. *BMC Health Serv Res* 2013;**13**:45. [PMID: 23379888]

Sterne 2011

Sterne JA, Effer M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated

March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Taher 2013

Taher AT, Viprakasit V, Musallam KM, Cappellini MD. Treating iron overload in patients with non-transfusion-dependent thalassemia. *American Journal of Hematology* 2013;**88**(5):409-15. [DOI: 10.1002/ajh.23405] [PMID: 23475638]

Thomas 1982

Thomas ED, Buckner CD, Sanders JE, Papayannopoulou T, Borgna-Pignatti C, De Stefano P, et al. Marrow transplantation for thalassaemia. *Lancet* 1982;**2**(8292):227-9. [PMID: 6124668]

van Besien 2000

van Besien K, Bartholomew A, Stock W, Peace D, Devine S, Sher D, et al. Fludarabine-based conditioning for allogeneic transplantation in adults with sickle cell disease. *Bone marrow transplantation* 2000;**26**(4):445-9. [PMID: 10982293]

Weatherall 2001

Weatherall DJ. Phenotype-genotype relationships in monogenic disease: lessons from the thalassaemias. *Nature Reviews Genetics* 2001;**2**(4):245-55. [PMID: 11283697]

Weatherall 2002

Weatherall DJ, Clegg JB. The Thalassaemia Syndromes. 4th edition. Oxford: Blackwell Science, 2002.

Weidlich 2016

Weidlich D, Kefalas P, Guest JF. Healthcare costs and outcomes of managing β-thalassemia major over 50 years in the United Kingdom. *Transfusion* 2016;**56**(5):1038-45. [DOI: 10.1111/trf.13513] [PMID: 27041389]

References to other published versions of this review

Jagannath 2011

Jagannath VA, Fedorowicz Z, Al Hajeri A, Hu N, Sharma A. Hematopoietic stem cell transplantation for people with ß-thalassaemia major. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No: CD008708. [DOI: 10.1002/14651858.CD008708.pub2]

Jagannath 2014

Jagannath VA, Fedorowicz Z, Al Hajeri A, Sharma A. Hematopoietic stem cell transplantation for people with ß-thalassaemia major. *Cochrane Database of Systematic Reviews* 2014, Issue 10. Art. No: CD008708. [DOI: 10.1002/14651858.CD008708.pub3]

Jagannath 2016

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

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	Participants in experimental and control cohorts were not randomised.
Irfan 2008	Not a prospective study.

BMT: bone marrow transplantation

APPENDICES

Appendix 1. Glossary

Term	Meaning
ablate	to remove or otherwise destroy the biological function of any part (e.g. bone marrow)

(Continued)

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
hemolytic anemia	anemia due to the abnormal breakdown of red blood cells
hemosiderosis	a form of iron overload disorder resulting in the accumulation of hemosiderin 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)

Appendix 2. Search strategies - trial registries

Registry	Search terms
ClinicalTrials.gov	Search terms: thalassemia AND transplant Study type: Interventional Studies
WHO ICTRP	Search terms: thalassemia AND transplant Recruitment status: ALL

Appendix 3. 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

WHAT'S NEW

Date	Event	Description
7 April 2021	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register identified 13 potentially-eligible references, five of these were additional references to an already-excluded trial (Chandy 2005); the remaining eight references were excluded after title or abstract review. The term 'thalassaemia major' has been replaced by the term 'transfusion-dependent thalassaemia' throughout the review.
7 April 2021	New citation required but conclusions have not changed	Minor changes have been made throughout many sections of the review.

HISTORY

Protocol first published: Issue 9, 2010
Review first published: Issue 10, 2011

Date	Event	Description
17 November 2016	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Haemoglobinopathies Trials Regsiter identified nine potentially relevant references. Eight were discarded and one was added to the 'Excluded studies' section of the review (Irfan 2008).
17 November 2016	New citation required but conclusions have not changed	Minor edits have been made throughout the review.
13 April 2015	Amended	Contact details updated.
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.
17 February 2014	New citation required but conclusions have not changed	Minor changes have been made throughout the text of this updated review.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
Protocol stage: draft the protocol	ZF/AH/VJ/NH/AS
Review stage: select which studies to include (2 + 1 arbiter)	ZF/AH/VJ
Review stage: extract data from studies (2 people)	ZF/AH/VJ
Review stage: enter data into RevMan	ZF/AH/VJ
Review stage: carry out the analysis	ZF/AH/VJ
Review stage: interpret the analysis	ZF/AH/VJ/NH/AS
Review stage: draft the final review	ZF/AH/VJ/NH/AS
Update stage (to 2016): update the review	ZF/AH/VJ/AS
Update stage (2018 onwards): update the review	AS/VJ/LP

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.

AS is the principal investigator of a clinical trial for gene therapy of sickle cell disease sponsored by Vertex Pharmaceuticals/CRISPR Therapeutics. The sponsor provides funding for the clinical trial which includes salary support paid to his institution. This is not related in any way to this work product.
AS also has research collaboration with Novartis pharmaceuticals for their sickle cell gene therapy clinical trial for which he is not financially compensated in any way.

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

A 'Summary of findings' section has been added to the methods section of the review.

The term 'thalassaemia major' has been replaced by the term 'transfusion-dependent thalassaemia' throughout the review. The title has been changed to 'Hematopoietic stem cell transplantation for people with β-thalassaemia'.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans