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Hematopoietic stem cell transplantation for Gaucher disease (Review)

Somaraju URR, Tadepalli K

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[Intervention Review]

Hematopoietic stem cell transplantation for Gaucher disease

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ABSTRACT

Background

Gaucher disease is the most common lysosomal storage disorder caused by a deficiency of the enzyme glucocerebrosidase. Current treatment of the disease involves a choice from enzyme replacement therapy, substrate reduction therapy and hemotopoietic stem cell transplantation (HSCT). HSCT is a high risk procedure with possible long-term benefits in the regression of skeletal and neurological changes in people with Gaucher disease. This is an update of a previously published Cochrane Review.

Objectives

To determine the role of HSCT in people with Gaucher disease in relation to: mortality risk associated with the procedure; efficacy in modifying the course of the disease; and arrest or regression of neurological manifestations in neuronopathic forms (types 2 and 3).

Search methods

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

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 19 January 2017.

We also searched the websites: www.clinicaltrials.gov; WHO International Clinical Trials Registry Platform portal and www.genzymeclinicalresearch.com. Date of most recent search of these sites: 02 March 2017.

Selection criteria

All randomised, quasi-randomised and controlled clinical trials comparing stem cell transplantation with enzyme replacement therapy, substrate reduction therapy, symptomatic treatment or no treatment in people with Gaucher disease of all ages.

Data collection and analysis

We independently assessed trials for inclusion, however, no relevant trials were identified.

Main results

Thirty two trials were identified by the searches; however, these were not suitable for inclusion in the review.

Authors' conclusions

HSCT is a form of treatment that offers the potential of permanent cure. However, there are no clinical trials that have assessed the safety and efficacy of this treatment in comparison to other conservative measures (enzyme replacement therapy, substrate reduction therapy) now in use.

There are no trials included in the review and we have not identified any relevant trials up to March 2017. We therefore do not plan to update this review until new trials are published.

PLAIN LANGUAGE SUMMARY

Stem cell transplantation for treating Gaucher disease

Review question

We reviewed the evidence about the effect of hematopoietic stem cell transplantation (HSCT) in people with Gaucher disease.

Background

Gaucher disease is an inherited disorder caused by a deficiency of the enzyme glucocerebrosidase. This leads to storage of complex lipids in some types of blood cells. Due to these abnormal cells people with Gaucher disease will have pain, fatigue, anemia, jaundice and bone damage. Some forms of Gaucher disease may also cause neurological damage. The treatment of Gaucher disease at present is mainly by enzyme replacement therapy which is expensive. In some severe cases HSCT is used to treat people with Gaucher disease. This is a high risk procedure sometimes leading to death of the individual.

Search date

The evidence is current to: 19 January 2017.

Study characteristics

We have not found any trials to show the effectiveness and the risks of the procedure in people with Gaucher disease.

Key results

We have not found any trials assessing the effectiveness and the risks of the procedure in people with Gaucher disease. There are no trials included in the review and we have not identified any relevant trials up to January 2017. We therefore do not plan to update this review until new trials are published.

Quality of the evidence

We have not found any trials assessing the effectiveness and the risks of the procedure in people with Gaucher disease.

BACKGROUND

Description of the condition

Gaucher disease is the most common lysosomal storage disorder. It is inherited as an autosomal recessive trait and characterised by the accumulation of glucocerebroside in the lysosomes due to a deficiency of the enzyme glucocerebrosidase (lysosomal acid β-glucosidase) (Beutler 2001). The glucocerebrosidase gene (GBA) has been mapped to chromosome one, band q21. More than 200 disease-causing mutations have been documented (Jmoudiak 2005).

The incidence of Gaucher disease in the general population is less than 1 in 30,000 to 40,000. It is more prevalent in people of Eastern European (Ashkenazi) Jewish descent with a prevalence of 1 in 1000 and a carrier frequency of 1 in 14 people (Mehta 2006). Classically three types of Gaucher disease have been identified based on the presence or absence of primary central nervous system involvement and the severity of the disease (Beutler 2001).

Non-neuronopathic form

Type 1 Gaucher disease

This is the most common form accounting for 90 to 95 per cent of the cases. It is characterised by onset in adulthood and by the absence of primary central nervous system involvement. However, some individuals, who have severe mutations, present with an onset in early childhood.

Neuronopathic forms

Type 2 Gaucher disease

This is characterised by severe neurological involvement and an onset during infancy.

Type 3 Gaucher disease

This is characterised by the onset of neurological disturbances in the first decade of life.

Types 2 and 3 are very rare and occur in less than 1 in 100,000 of the population. The prototype of type 3 Gaucher disease is found with high frequency in the Norbottnian population of northern Sweden (Mehta 2006).

The pathophysiological feature of Gaucher disease is the presence of Gaucher cells derived from the monocyte-macrophage system. Gaucher cells are present throughout the body, but the largest numbers are found in the spleen, liver, bone marrow, and lymph nodes causing enlargement and dysfunction of these organs resulting in clinical manifestations. Typically the infant is normal at birth, with clinical features only becoming apparent as the abnormal substrate accumulates. Bleeding due to thrombocytopenia (low platelet count), anemia and hepatosplenomegaly (abnormal enlargement of the liver and spleen) are the common early features. Bone involvement is common but is not always associated with symptoms. The symptoms of bone disease range from mild pain to severe bone crises. Growth retardation is seen in moderate to severe forms of disease. The neurological symptoms seen in types 2 and 3 include oculomotor apraxia (difficulty moving the eyes), opisthotonus (extreme backward arching of the spine), bulbar signs (problems with breathing, swallowing and talking) and seizures (Beutler 2001; Beutler 2006). Type 1 Gaucher disease has a broad spectrum of severity ranging from individuals who have been diagnosed in their eighth or ninth decade to children who die of complications during their first or second decade. Most infants with type 2 disease die within the first two years of life; and the severity of type 3 is intermediate between types 1 and 2 (Beutler 2001). A confirmed diagnosis can be made by measuring the glucocerebrosidase activity of peripheral blood leucocytes or cultured skin fibroblasts. Alternatively DNA analysis can be used to diagnose Gaucher disease and also to establish a disease prognosis (Beutler 2006).

Description of the intervention

The treatment of Gaucher disease before the 1990s was essentially symptomatic. The advent of enzyme replacement therapy (ERT) has revolutionised the treatment approach to this disorder. Human placental β-glucocerebrosidase was modified to expose variable numbers of mannose residues, so that it can be targeted to the macrophages (Danuta 1995). This is the preferred form of treatment for symptomatic individuals with type 1 disease. Treatment results in significant regression of disease in these individuals and has very few side effects (Morales 1996). The main drawbacks of ERT are that weekly infusions of the enzyme are required, and the treatment is very expensive. The cost of therapy for a child weighing 50 kg (at a dose of 130 units per kg per month) is approximately USD 300,000 per year for the medication alone (Beutler 2005). Moreover, the enzyme does not cross the blood brain barrier so it cannot be effective in types 2 and 3 diseases to improve neurological symptoms (Erikson 1993; Zimran 1995).

Since the pathophysiology of Gaucher disease is due to accumulation of lipid laden macrophages, bone marrow transplantation was thought of as a logical treatment for the disease. The first allogeneic bone marrow transplantation was done in the 1980s. The individual died due to sepsis but had shown regression of disease manifestations (Rappeport 1984). Since then many people have undergone hematopoietic stem cell transplantation (HSCT) (August 1984; Chan 1994; Hobbs 1987; Ringden 1988; Ringden 1995; Svennerholm 1991; Tsai 1992). Initially the HSCT was performed using donor bone marrow from siblings with an identical tissue type. With major improvements in the various areas of transplantation, the choice of donor cells has now expanded to include peripheral blood stem cells (PBSC) mobilised into the blood of the donor using granulocyte colony stimulating factor (G-CSF), marrow from matched or mismatched family members or unrelated donors and cord blood from siblings and unrelated babies. There is also increasing use of haploidentical tissue from parents.

How the intervention might work

The outcomes of HSCT are affected by numerous aspects of the transplant such as donor enzyme level, degree and persistence of donor chimerism, and post-transplant complications (Peters 2003; Steward 2005). Benefit of transplantation varies between organ systems. Hematological and physical improvement is rapid and sustained. Reticuloendothelial organs, such as the liver and spleen regress within a few months (Peters 2003) and there is evidence that most of the skeletal changes seen in Gaucher disease regress (Starer 1987). The evidence on the beneficial effect of bone marrow transplantation on the regression of the neurological disease in people with types 2 and 3 is conflicting (Ringden 1988;

Svennerholm 1991; Tsai 1992). The response is slow and the effectiveness appears to depend on the age of the individual, severity of the disease and its progression at the time of treatment.

Newer modes of Intervention

Besides ERT and HSCT there are a few other promising treatments. A recently introduced therapy is substrate reduction therapy (SRT). Miglustat (Zavesca, N-butyl deoxynojirimycin, OGT 918) has been licensed for the treatment of Gaucher disease in those who are not able to receive ERT. This compound inhibits glucosylceramide synthase, preventing new synthesis of glucosylceramide. The clinical trials show it is effective in most people with mild and stable disease, but is less well-tolerated. The drug crosses the blood brain barrier, and its effectiveness in the treatment of the types 2 and 3 Gaucher disease is under investigation. A new generation of therapeutic recombinant enzymes is under development which has an in-frame fusion to HIV-1 trans-activator protein transduction domain (TAT). The TAT modification improves the delivery of the enzyme to cells without mannose -specific endocytic receptors on the plasma membrane. Another option is the use of more specific small molecules that inhibit substrate synthesis (substrate deprivation), or act as chaperones to increase the activity of the enzyme (enzyme enhancement therapy). Various gene transfer methods are also in different trial phases (Schmitz 2007).

Why it is important to do this review

HSCT is a less expensive procedure that offers the potential of permanent cure when compared to other conservative measures now in use (ERT, SRT). However, the procedure is associated with a mortality ranging from less than 5% to more than 10% depending on the availability of human leucocyte antigen (HLA)-matched sibling and the source of the stem cells (Kumar 2007). The mortality is expected to be higher in the severely compromised individuals with Gaucher disease. The choice between HSCT and conservative measures to treat people with Gaucher disease depends on the assessment of the long-term benefits of HSCT over the significant mortality and morbidity associated with the procedure. Another issue to be resolved in this area is whether HSCT can correct metabolic abnormalities of the central nervous system in individuals with type 2 and 3 Gaucher disease. This is an updated version of a previously published review (Somaraju 2008b; Somaraju 2010; Somaraju 2012).

OBJECTIVES

To determine the role of HSCT in people with Gaucher disease in relation to:

1. mortality risk associated with the procedure;
2. efficacy in modifying disease course, and;
3. arrest or regression of neurological manifestations in neuronopathic forms (types 2 and 3).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). Non-randomised allocation to HSCT due to availability of HLA-matched donor was considered acceptable. We planned to include controlled clinical trials (CCTs) including quasi-randomised controlled trials if the controls were sufficiently comparable to the treatment group.

Types of participants

Children and adults diagnosed with Gaucher disease by measuring glucocerebrosidase levels in peripheral blood leucocytes or fibroblasts or by analysis of DNA.

Types of interventions

HSCT compared with ERT, SRT, symptomatic treatment or no treatment.

Types of outcome measures

We planned to group the outcome data into those measured at 3, 6, and 12 months and annually thereafter. We also planned to collect change from baseline data for these outcomes where reported. Some treatment effects may show progressively higher efficiency in causing a regression of the disease and this we think can best be established by comparison of treatment effect from baseline.

Primary outcomes

1. Hematological assessment - hemoglobin concentration and platelet counts
2. Visceral assessment - liver and spleen volumes by volumetric computer tomography (CT) or magnetic resonance imaging (MRI) or ultrasound
3. Mortality and morbidity
   a. overall mortality
   b. transplant-related mortality
   c. transplant-related morbidity

Secondary outcomes

1. Skeletal system assessment - osteoporosis and marrow infiltration by magnetic resonance imaging (MRI) or plain radiography or other imaging techniques
2. Neuropsychiatric evaluation using Weschler scale or any other comparable scale
3. Evaluation of changes in neurophysiologic parameters such as electroencephalogram (EEG), MRI Brain, visual evoked potentials (VEP), brainstem auditory evoked responses (BAER)
4. Growth and pubertal development
5. Quality of life
6. Duration of hospitalisation
7. Complications due to transplantation

Search methods for identification of studies

There will be no restrictions regarding language or publication status.

Electronic searches

Relevant trials were identified from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register using the term: gaucher.

The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), weekly searches of MEDLINE and the

prospective handsearching of one journal - *Journal of Inherited Metabolic Disease*. Unpublished work is identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. 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.

Date of the last search of the Group's Inborn Errors of Metabolism Trials Register: 19 January 2017.

We also conducted searches of the websites: www.clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP) portal; and www.genzymeclinicalresearch.com. Please refer to the appendices section of the review for further details (Appendix 1; Appendix 2; Appendix 3).

Date of most recent search of these sites: 02 March 2017.

Data collection and analysis

Selection of studies

We undertook new searches for the review in January and March 2017 and identified 17 new trials, taking the total number of trials identified to 32. Two authors (US and KT) independently applied the inclusion criteria to the 32 trials identified by the searches. We performed this without any blinding. We planned to resolve any disagreements arising through discussions. However, none of the trials identified were relevant to the review.

Data extraction and management

As no trials have yet been included in the review, we are unable to carry out any analysis. If we find trials for future updates of this review, we will independently extract data from the selected trials using standardised data extraction forms.

Assessment of risk of bias in included studies

We will assess every trial using a simple form and will follow the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions 5.3* (Higgins 2011).

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

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

Measures of treatment effect

In future updates, if we are able to include any trials, for dichotomous outcomes, we plan to estimate treatment effects using the risk ratio (RR). For continuous outcomes we plan to record either mean relative change from baseline for each group or mean post-treatment or post-intervention values and standard deviation. If standard errors are reported (and if possible) we plan to convert these to standard deviations. We plan to calculate a pooled estimate of treatment effect by calculating the mean difference. Time-to-event data will be calculated as hazard ratios with 95% confidence intervals (Parmar 1998).

Assessment of heterogeneity

We plan to quantify the impact of statistical and clinical heterogeneity in the meta-analysis using a measure (I^2) of the degree of inconsistency in the studies' results (Higgins 2003). This measure describes the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins 2003). The values of I^2 lie between 0% and 100%, and a simplified categorization of heterogeneity that we plan to use is (Higgins 2003):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We will use a funnel plot to assess whether the review is subject to publication bias. If asymmetry is detected we will also assess other possible causes.

Data synthesis

If significant heterogeneity is identified we will use the random-effects model. If we do not identify significant heterogeneity we will compute pooled estimates of the treatment effect for each outcome under a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

If we find sources of heterogeneity and if there are sufficient data, we will conduct meta-analysis by subgroups. We will investigate the possible causes of this further by exploring the impact of the different types of Gaucher disease, severity of the disease at baseline, and a difference in the dosage of enzyme in the individuals.

Sensitivity analysis

We plan to perform a sensitivity analysis based on the methodological quality of trials, including and excluding quasi-RCTs and CCTs.

RESULTS

Description of studies

We found no trials that were eligible for inclusion in this review. The 32 trials listed as excluded studies were not eligible for all or some of the following reasons: not a RCT or quasi-RCT or CCT (Baker 1999; Barranger 1999; Mankoski 2014; Orchard 2008) or the interventions were not relevant (Abbas 2015; Almon 2008; Charrow 2014; Cox 2014; de Fost 2007; Elstein 2001; Elstein 1998; Garcia 2014; Gonzales 2010; Grabowski 1995; Kishnani 2009; Lukina 2013; Lukina 2016; Medrano-Engay 2013; Mehta 2008; Mistry 2013; Nuzhnyi 2014; Schiffmann 2008; Turpault 2015; Weinreb 2008; Wenstrup 2004; Zimran 2011; Zimran 2012; Zimran 2013; Zimran 2014; Zimran 2015; Zimran 2016a; Zimran 2016b). Please see the 'Characteristics of excluded studies' table for more details.

Risk of bias in included studies

We found no trials eligible for inclusion in this review.

Effects of interventions

We found no trials eligible for inclusion in this review.

DISCUSSION

We have not found any relevant RCTs, quasi-RCTs or CCTs assessing the role of HSCT for treating Gaucher disease.

At present HSCT is a treatment that can provide a permanent source of enzyme to people with Gaucher disease and is a considerably less expensive procedure when compared to the more commonly used intervention, ERT. A number of case-series reports have shown that, where engraftment takes place, HSCT leads to a favorable clinical outcome with a growth spurt, reversal of organomegaly, and a possible regression of skeletal changes. People with type 3 Gaucher disease showed no further neurological deterioration. One non-randomised study has suggested that HSCT may be more effective than ERT at currently used dosage levels, in reducing total body stores of glucocerebroside (Young 1997).

However, the important limitations of HSCT are the mortality and morbidity associated with the procedure and the non-availability of HLA-matched donors. For these reasons HSCT is postponed as a treatment until very late in the course of disease, when a cure is less likely. But the recent technological advances in the field of transplantation have expanded the sources of stem cells and also reduced the risks associated with the procedure. It is therefore important to re-evaluate the risks and benefits of HSCT in comparison with the more conservative but noncurative options such as ERT and substrate reduction therapy in the treatment of people with Gaucher disease. Until adequate data from appropriate clinical trials become available, clinicians will need to balance the possible benefits against the possible risks of transplantation.

AUTHORS' CONCLUSIONS

Implications for practice

No randomised controlled trials (RCTs), quasi-RCTs or controlled clinical trials (CCTs) on the efficacy of hemotopoietic stem cell transplantation (HSCT) were identified for inclusion in the review. The research evidence on which to base clinical decisions is limited to case reports. Given that there are no trials included in the review and we have not identified any relevant trials up to January 2017 we do not plan to update this review until new trials are published.

Implications for research

No RCTs, quasi-RCTs or CCTs on the efficacy of HSCT were identified for inclusion in the review. There is a need for a well-designed RCT to evaluate the benefits and risks of HSCT in comparison to other prevalent forms of treatment in people with Gaucher disease.

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REFERENCES

References to studies excluded from this review

Abbas 2015 *{published data only}*

Abbas R, Park G, Damle B, Chertkoff R, Alon S. Pharmacokinetics of Novel Plant Cell-Expressed Taliglucerase Alfa in Adult and Pediatric Patients with Gaucher Disease. *PLoS ONE [electronic Resource]* 2015;**10**(6):e0128986. [CENTRAL: 1135338]

Almon 2008 *{published data only}*

Almon E. Novel enzyme replacement therapy for Gaucher disease; on-going phase 3 clinical trial with recombinant human glucocerebrosidase expressed in plant cells. In: Proceedings of the 8th European Working Group on Gaucher Disease (EWGGD); 2008 June 4-7; Budapest, Hungary. 2008:18.

Baker 1999 *{unpublished data only}*

Baker KS. Study of pulmonary complications in Pediatric Patients With Storage Disorders undergoing Allogeneic Hematopoietic stem cell transplantation. www.clinicaltrials.gov.

Barranger 1999 *{unpublished data only}*

Barranger J. Phase I study of Retrovirally Mediated Transfer of the Human Glucocerebrosidase Gene into peripheral Blood Stem Cells for Autologous Transplantation in Patients With Type I Gaucher disease. www.clinicaltrials.gov.

Charrow 2014 *{published data only}*

Charrow J, Ida H, Hollak C, Amato D, Cravo R, Kawaguchi O, et al. EDGE: A Phase 3 study evaluating once versus twice daily dosing of eliglustat in patients with Gaucher disease type 1: Interim results from the lead-in-period. *Molecular Genetics and Metabolism* 2014;**111**(2):S30. [ABSTRACT NO.: 41] [CENTRAL: 1073796] [EMBASE: 71805024]

Cox 2014 *{published data only}*

Cox TM, Drelichman G, Balwani M, Burrow TA, Lukina E// Rosenbloom B, Gaemers SJM, et al. Four-year follow-up form the ENCORE trial: a randomized, controlled, non-inferiority study comparing eliglustat to imiglucerase in patients with gaucher disease type 1 stabilized on enzyme replacement therapy. *Molecular Genetics and Metabolism* 2016;**117**(2):S37. [ABSTRACT NO.: 71] [CENTRAL: 1262067]

Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, et al. Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial. *Lancet* 2015;**385**(9985):2355-62. [CENTRAL: 1083551] [EMBASE: 2015864407] [PMID: 25819691]

* Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, et al. ENCORE: a randomized, controlled, open label non-inferiority study comparing eligustat to imiglucerase in Gaucher disease type 1 patients stabilized on enzyme replacement therapy: 24-month results. *Journal of Inherited Metabolic Disease* 2014;**37 Suppl 1**:S157. [ABSTRACT NO.: P-436] [CENTRAL: 1000858]

Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM, et al. The ENCORE trial: outcomes in adult patients with gaucher disease type 1 previously stabilzed on enzyme therapy after 4 years of treatment with eliglustat. *Journal of Inherited Metabolic Disease* 2016;**39 Suppl 1**:S198. [ABSTRACT NO.: P-476] [CENTRAL: 1262069]

Cox TM, Drelichman G, Cravo R. Erratum: Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: A phase 3, randomised, open-label, non-inferiority trial (Lancet (2015) 385 (2355-2362)). *Lancet* 2015;**385**(9985):2354. [CENTRAL: 1102818] [EMBASE: 2015124425]

Cox TM, Drelichman GI, Cravo R, Balwani M, Burrow TA, Martins AM, et al. ENCORE, a randomized, controlled, open-label non-inferiority study comparing eligustat to imiglucerase in Gaucher disease type 1 patients stabilized on enzyme replacement therapy: 24 month results. *Molecular Genetics and Metabolism* 2015;**114**:S33. [ABSTRACT NO.: 56] [CENTRAL: 1046746]

Giraldo P, Pleat R, Angell J, Rosenbloom BE, Ibrahim J. Stability is maintained in adult patients with Gaucher disease type 1 (GD1) switched from velaglucerase to eliglustat: A sub-analysis of the eliglustat, phase 3 ENCORE trial. *Journal of Inherited Metabolic Disease* 2015;**38**(1 Suppl):S296-7. [ABSTRACT NO.: P-610] [CENTRAL: 1130482] [EMBASE: 71999143]

Rosenbloom BE, Cox TM, Drelichman GI, Cravo R, Balwani M, Burrow TA, et al. Encore - a randomized, controlled, open-label non-inferiority study comparing eliglustat to imiglucerase in gaucher disease type 1 patients stabilized on enzyme replacement therapy: 24-month results. *Blood* 2014;**124**(21). [ABSTRACT NO.: 1406]

de Fost 2007 *{published data only}*

de Fost M, Aerts JM, Groener JE, Maas M, Akkerman EM, Wiersma MG et al. Low frequency maintenance therapy with imiglucerase in adult type 1 Gaucher disease: a prospective randomised controlled trial. *Haematologica* 2007;**92**(2):215-21.

Elstein 1998 *{published data only}*

Elstein D, Abrahamov A, Hadas-Halpern I, Meyer A, Zimran A. Low-dose low frequency imiglucerase as a starting regimen of enzyme replacement therapy for patients with type 1 Gaucher disease. *QJM:Monthly Journal of the Association of Physicians* 1998;**91**(7):483-8.

Elstein 2001 *{published data only}*

Elstein D, Heitner R, Dweck A, Attias D, Atarescu G, Zimran A. OGT918 as substrate reduction therapy in type 1 gaucher disease. In: Proceedings of the 6th Meeting of the European Hematology Association. Frankfurt, Germany, 2001. [ABSTRACT NO.: 212]

Garcia 2014 *{published data only}*

Garcia CS, Santin J, Mello AS, Pires GD, Peres A, Coelho JC. Gaucher disease: levels of inflammatory factors in patients with and without enzyme replacement therapy. *Journal of Inherited Metabolic Disease* 2014;**37 Suppl 1**:S144. [ABSTRACT NO.: P-384] [CENTRAL: 1000861]

Gonzales 2010 *{published data only}*

Gonzales DE, Ben Dridi MF, Lukina E, Kisinovsky I, Ben Turkia H, Elstein D et al. Clinically significant hemoglobin response observed within 3 months following treatment with velaglucerase alfa in patients with type 1 gaucher disease. *Journal of Inherited Metabolic Disease* 2010;**33**(Suppl 1):S139. [ABSTRACT NO.: 442-P]

Grabowski 1995 *{published data only}*

Grabowski GA, Barton NW, Pastores G, Dambrosia JM, Banerjee TK, McKee MA et al. Enzyme therapy in gaucher disease type 1: comparative efficacy of mannose terminated glucocerebrosidase from natural and recombinant sources. *Annals of Internal Medicine* 1995;**122**(1):33-9.

Kishnani 2009 *{published data only}*

Kishnani PS, DiRocco M, Kaplan P, Mehta A, Pastores GM, Smith SE et al. A randomized trial comparing the efficacy and safety of imiglucerase (Cerezyme) infusions every 4 weeks versus every 2 weeks in the maintenance therapy of adult patients with Gaucher disease type 1. Molecular Genetics and Metabolism 2009;**96**(4):164-70.

Lukina 2013 *{published data only}*

Lukina E, Dridi M, Amato D, Baris H, Dasouki M, Ghosn M, et al. A phase3, randomized, double blind, placebo controlled, multi center study (ENGAGE) to investigate the efficacy and safety of eliglustat in patients with gaucher disease type 1: 9 month results. *Haematologica* 2013;**98 Suppl 1**:405-6. [ABSTRACT NO.: P982] [CENTRAL: 1057939] [EMBASE: 71696827]

Lukina 2016 *{published data only}*

Lukina E, Cox T, Mistry P, Weinreb N, Angell J, Gaemers S, et al. Long-term hematologic, biomarker, and bone response to oral eliglustat in patients with gaucher disease type 1: results from a phase 2 and two phase 3 trials. *Haematologica* 2016;**101 Suppl 1**:194, Abstract no: S519. [CENTRAL: 1262068]

Mankoski 2014 *{published data only}*

* Mankoski R, Taylor JS, Angell J, Peterschmitt MJ. Clinical response to eliglustat in treatment-naive patients with Gaucher disease type 1: post-hoc comparison to imiglucerase in a real-world setting. *Journal of Inherited Metabolic Disease* 2014;**37 Suppl 1**:S156. [ABSTRACT NO.: P-430] [CENTRAL: 1000859]

Peterschmitt MJ, Taylor JS, Angell J, Ibrahim J, Genzyme. Clinical response to eliglustat in treatment-naive patients with Gaucher disease type 1: Post-hoc comparison to imiglucerase in a real-world setting. *Molecular Genetics and Metabolism* 2015;**114**(2):S93. [ABSTRACT NO.: 204] [CENTRAL: 1077598] [EMBASE: 71804744]

Medrano-Engay 2013 *{published data only}*

Medrano-Engay B, Irun MP, Sarria L, Alfonso P, Pocovi M, Giraldo P. Analysis of efficacy and safety of two iron chelators in type 1 Gaucher disease patients with iron overload. *Molecular Genetics and Metabolism* 2013;**108**(2):S64-5. [ABSTRACT NO.: 151] [CENTRAL: 1073856] [EMBASE: 71805414]

Mehta 2008 *{published data only}*

Mehta A. A multicentre, randomised, dose frequency study of the safety and efficacy of cerezyme infusions every 4 weeks versus every 2 weeks in the maintenance therapy of patients with type 1 gaucher disease. Proceedings of the 8th European Working Group on Gaucher Disease (EWGGD); 2008 June 4-7th; Budapest, Hungary 2008:11.

Mistry 2013 *{published data only}*

Mehta A, Mistry P, Lukina E, Ben Turkia H, Baris H, Ghosn M, et al. Effects of oral eliglustat on bone parameters in treatment naive patients with Gaucher disease type 1 (GD1): 18-month results from the phase 3, randomized, placebo controlled ENGAGE trial. *Journal of Inherited Metabolic Disease* 2015;**38**(1 Suppl):S297-8. [ABSTRACT NO.: P-614] [CENTRAL: 1130481] [EMBASE: 71999146]

Mistry P, Amato DJ, Dasouki M, Packman S, Pastoes GM, Assouline S, et al. ENGAGE - A phase 3, randomized, double-blind, placebo controlled, multi-center study to investigate the efficacy and safety of eligustat in adults. *Molecular Genetics and Metabolism* 2015;**114**:S81. [ABSTRACT NO.: 176] [CENTRAL: 1046747]

* Mistry P, Lukina E, Ben Dridi M-F, Amato D, Baris H, Dasouki M, et al. A phase 3, randomized, double-blind, placebo-controlled, multi-center study to investigate the efficacy and safety of eliglustat in patients with Gaucher disease type 1 (ENGAGE): Results after 9 months of treatment. *Molecular Genetics and Metabolism* 2013;**108**(2):S66-7. [ABSTRACT NO.: 157] [CENTRAL: 1073855] [EMBASE: 71805420]

Mistry PK, Lukina E, Ben Turkia H, Amato D, Baris H, Dasouki M, et al. Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial. *JAMA* 2015;**313**(7):695-706. [CENTRAL: 1050650] [JID: 7501160] [PMID: 25688781] [SI: ClinicalTrials.gov/NCT00891202]

Mistry PK, Lukina E, Ben Turkina H, Baris H, Ghosn M, Mehta A, et al. ENGAGE: a phase 3, randomized, double-blind, placebo-controlled, multi-center study to investigate the efficacy and safety of eliglustat in adults with Gaucher disease type 1: 18-month results. *Journal of Inherited Metabolic Disease* 2014;**37 Suppl 1**:S159. [ABSTRACT NO.: P-441] [CENTRAL: 1000857]

Pleat R, Cox TM, Burrow TA, Giraldo P, Goker-Alpan O, Rosenbloom BE, et al. Stability is maintained in adults with Gaucher disease type 1 switched from velaglucerase alfa to eliglustat or imiglucerase: A sub-analysis of the eliglustat ENCORE trial. *Molecular Genetics and Metabolism Reports* 2016;**9**:25-8. [CENTRAL: 1262066] [PMID: 27722092]

Shankar S, Lukina E, Amato DJ, Dasouki M, Packman S, Pastores GM, et al. Engage: a phase 3, randomized, double-blind, placebo-controlled, multi-center study to investigate the efficacy and safety of eliglustat in adults with gaucher disease type 1: 9 month results. *Blood* 2013;**122**(21). [ABSTRACT NO.: 2275] [CENTRAL: 1135337]

Nuzhnyi 2014 *{published data only}*

Nuzhnyi EP, Emelyanov AK, Bukina TM, Salogub GN, Yakimovskii AF, Pchelina SN, et al. Plasma oligometric alpha-synuclein levels in patients with Gaucher disease is attentuated

by duration of enzyme-replacement therapy. *Journal of Inherited Metabolic Disease* 2014;**37 Suppl 1**:S160. [ABSTRACT NO.: P-446] [CENTRAL: 1000856]

Orchard 2008 *{unpublished data only}*

Orchard P. Treatment of Lysosomal and Peroxisomal Inborn Errors of Metabolism by Bone Marrow Transplantation. www.clinicaltrials.gov.

Schiffmann 2008 *{published data only}*

Schiffmann R, Fitzgibbon EJ, Harris C, DeVile C, Davies EH, Abel L, et al. Randomized, controlled trial of miglustat in Gaucher's disease type 3. Annals of Neurology 2008;**64**(5):514-22.

Turpault 2015 *{published data only}*

Turpault S, Meng Z, Wang S, Von Moltke L. CYP2D6 phenotype-based dosing of eliglustat. *Molecular Genetics and Metabolism* 2015;**114**(2):S118. [ABSTRACT NO.: 269] [CENTRAL: 1073776] [EMBASE: 71804809]

Weinreb 2008 *{published data only}*

Weinreb NJ. A phase 2 clinical trial of the pharmacological chaperone AT2101 for the treatment of gauchers disease. In: Proceedings of the 8th European Working Group on Gaucher Disease (EWGGD); 2008 June 4-7; Budapest, Hungary. 2008:14.

* Weinreb N on behalf of AT2101 Study Group. A phase 2 clinical trials of the pharmacological chaperone AT2101 for the treatment of Gaucher disease. *Journal of Inherited Metabolic Disease* 2008;**108**. [ABSTRACT NO.: 427-P]

Wenstrup 2004 *{published data only}*

Wenstrup RJ, Bailey L, Grabowski GA, Moskovitz J, Oestrich AE, Wu W et al. Gaucher disease: alendronate disodium improves bone mineral density in adults receiving enzyme therapy. *Blood* 2004;**104**(5):1253-7.

Zimran 2011 *{published data only}*

Zimran A, Brill-Almon E, Chertkoff R, Petakov M, Blanco-Favela F, Munoz ET et al. Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease. Blood 2011;**118**(22):5767-73.

Zimran 2012 *{published data only}*

Zimran A, Kabra M, Giraldo P, Dridi M-FB, Elstein D, Gupta N, et al. Safety and efficacy of velaglucerase alfa in patients with type 1 gaucher disease: 2 years of treatment in phase III trials and an extension study [abstract]. *Molecular Genetics and Metabolism* 2012;**105**(2):S69. [CENTRAL: 1034474] [EMBASE: 70702137]

Zimran 2013 *{published data only}*

Zimran A, Mehta A, Giraldo P, Rosenbaum H, Giona F, Amato DJ, et al. Long-term safety and efficacy data of taliglucerase alfa, a Plant cell-expressed recombinant glucocerebrosidase, in the treatment of naive Gaucher disease patients: 36-Month Results. *Molecular Genetics and Metabolism* 2013;**108**(2):S102. [ABSTRACT NO.: 266] [CENTRAL: 1073852] [EMBASE: 71805529]

Zimran 2014 *{published data only}*

Zimran A, Duran G, Mehta A, Giraldo P, Rosenbaum H, Giona F, et al. Taliglucerase alfa 36-month clinical safety and efficacy in treatment-naive patients. *Journal of Inherited Metabolic Disease* 2014;**37 Suppl 1**:S155. [ABSTRACT NO.: P-428] [CENTRAL: 1000860]

Zimran 2015 *{published data only}*

* Zimran A, Gonzalez-Rodriguez DE, Abrahamov A, Cooper PA, Varughese S, Paz A, et al. Comparison of taliglucerase alfa 30 U/Kg and 60 U/Kg in treatment-naive pediatric patients with Gaucher disease. *Journal of Inherited Metabolic Disease* 2015;**38**(1 Suppl):S302-3. [ABSTRACT NO.: P-626] [CENTRAL: 1130480] [EMBASE: 71999158]

Zimran A, Gonzalez-Rodriguez DE, Abrahamov A, Cooper PA, Varughese S, Paz A, et al. Comparison of taliglucerase alfa 30 U/kg and 60 U/kg in treatment-naive pediatric patients with Gaucher disease. *Molecular Genetics and Metabolism* 2015;**114**(2):S128-9. [ABSTRACT NO.: 292] [CENTRAL: 1073775] [EMBASE: 71804832]

Zimran A, Gonzalez-Rodriguez DE, Abrahamov A, Cooper PA, Varughese S, Paz A, et al. Long-term safety and efficacy of taliglucerase alfa in pediatric patients with Gaucher disease who were treatment-naive previously treated with immiglucerase. *Molecular Genetics and Metabolism* 2015;**114**(2):S129. [ABSTRACT NO.: 293] [CENTRAL: 1077596] [EMBASE: 71804833]

Zimran A, Gonzalez-Rodriguez DE, Abrahamov A, Elstein D, Paz A, Brill-Almon E, et al. Safety and efficacy of two dose levels of taliglucerase alfa in pediatric patients with Gaucher disease. *Blood Cells, Molecules & Diseases* 2015;**54**(1):9-16. [PMID: 25453586]

Zimran 2016a *{published data only}*

Zimran A, Duran G, Mehta A, Giraldo P, Rosenbaum H, Giona F, et al. Long-term efficacy and safety results of taliglucerase alfa up to 36 months in adult treatment-naive patients with Gaucher disease. *American Journal of Hematology* 2016;**91**(7):656-60. [PMID: 27174694]

Zimran 2016b *{published data only}*

Zimran A, Duran G, Giraldo P, Rosenbaum H, Giona F, Petakov M, et al. Long-term efficacy and safety results of taliglucerase alfa through 5years in adult treatment-naive patients with Gaucher disease. Blood Cells, Molecules & Diseases (in press). [PMID: 27499018]

Additional references

August 1984

August CS, Palmieri M, Nowell P, Elkins WL, D'Angio G, Glew RH, et al. Bone marrow transplantation (BMT) in Gaucher's disease. *Paediatric Research* 1984;**18**:236A.

Beutler 2001

Beutler E, Grabowski GA. Gaucher Disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, Vogelstein B, editors(s). The Metabolic and Molecular Bases of Inherited

Disease. 8th edition. Vol. **III**. New York: McGraw-Hill, 2001:3635-68.

Beutler 2005

Beutler E. The treatment of Gaucher disease in countries with limited health care resources. *Indian Journal of Human Genetics* 2005;**11**(3):121-7.

Beutler 2006

Beutler E. Gaucher disease: multiple lessons from a single gene disorder. *Acta Paediatrica* 2006;**Suppl 451**:103-9.

Chan 1994

Chan KW, Wong LTK, Applegarth D, Davidson AGF. Bone marrow transplantation in Gaucher's disease: effect of mixed chimeric state. *Bone Marrow Transplantation* 1994;**14**(2):327-30.

Danuta 1995

Danuta B, Beutler E. Gaucher Disease. *Medicine* 1995;**74**(6):305-23.

Erikson 1993

Erikson A, Johansson K, Monsson JE, Svennerholm L. Enzyme replacement therapy of infantile Gaucher disease. *Neuropediatrics* 1993;**24**(4):237-8.

Higgins 2003

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

Higgins 2011

Higgins JPT, Altman DG, Sterne JAC on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group, editor(s). Chapter 8: Searching for 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 handbook.cochrane.org.

Hobbs 1987

Hobbs JR, Jones KH, Shaw PJ, Lindsay I, Hancock M. Beneficial effect of pre-transplant splenectomy on displacement bone marrow transplantation for Gaucher's syndrome. *Lancet* 1987;**1**(8542):1111-5.

Jmoudiak 2005

Jmoudiak M, Futerman AH. Gaucher disease: pathological mechanisms and modern management. *British Journal of Haematology* 2005;**129**(2):178-88.

Kumar 2007

Kumar L. Haematopoietic stem cell transplantation: current status. *National Medical Journal of India* 2007;**20**(3):128-37.

Mehta 2006

Mehta A. Epidemiology and natural history of Gaucher's disease. *European Journal of Internal Medicine* 2006;**17**:S2-S5.

Morales 1996

Morales LE. Gaucher's Disease: A Review. *Annals of Pharmacotherapy* 1996;**30**(4):381-8.

Parmar 1998

Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival end-points. *Statistics in Medicine* 1998;**17**(24):2815-34.

Peters 2003

Peters C, Steward CG. Haematopoietic stem cell transplantation for Inherited metabolic diseases: an overview of outcomes and practice guidelines. *Bone Marrow Transplantation* 2003;**31**(4):229-39.

Rappeport 1984

Rappeport JM, Ginns EI. Bone-marrow transplantation In severe Gaucher's disease. *New England Journal of Medicine* 1984;**311**(2):84-8.

Ringden 1988

Ringden O, Groth CJ, Erikson A, Backman L, Granqvist S, Mansson JE et al. Long-term follow-up of the first successful bone marrow transplantation in Gaucher disease. *Transplantation* 1988;**46**(1):66-70.

Ringden 1995

Ringden O, Groth CG, Erikson A, Granqvist S, Mansson JE, Sparrelid E. Ten years experience of bone marrow transplantation for gaucher disease. *Transplantation* 1995;**59**(6):864-70.

Schmitz 2007

Schmitz J, Poll LW, Dahl SV. Therapy of adult Gaucher disease. *Haematologica* 2007;**92**(2):148-52.

Starer 1987

Starer F, Sargent JD, Hobbs JR. Regression of the radiological changes of Gaucher's disease following bone marrow transplantation. *British Journal of Radiology* 1987;**60**(720):1189-95.

Steward 2005

Steward CG, Jarisch A. Haemopoietic stem cell transplantation for genetic disorders. *Archives of Disease in Childhood* 2005;**90**(12):1259-63.

Svennerholm 1991

Svennerholm L, Erikson A, Groth CG, Ringden O, Mansson JE. Norbottnian type of Gaucher disease - Clinical, Biochemical and Molecular Biology aspects: Successful treatment with Bone marrow transplantation. *Developmental Neuroscience* 1991;**13**(4-5):345-51.

Tsai 1992

Tsai P, Lipton JM, Sahdev I, Najfeld V, Rankin LR, Slyper AH et al. Allogeneic Bone marrow transplantation in Severe Gaucher disease. *Pediatric Research* 1992;**31**(5):503-7.

Young 1997

Young E, Chatterton C, Vellodi A, Winchester B. Plasma chitotriosidase activity in Gaucher disease patients who have been treated either by bone marrow transplantation or by enzyme replacement therapy with alglucerase. *Journal of Inherited Metabolic Disease* 1997;**20**(4):595-602.

Zimran 1995

Zimran A, Elstein D, Abrahamov A. Enzyme replacement therapy in type 1 and type 3 Gaucher's disease. *Lancet* 1995;**345**(8947):451-2.

References to other published versions of this review

Somaraju 2008a

Somaraju UR, Tadepalli K. Hematopoietic stem cell transplantation for Gaucher disease. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No: CD006974. [DOI: 10.1002/14651858.CD006974]

Somaraju 2008b

Somaraju UR, Tadepalli K. Hematopoietic stem cell transplantation for Gaucher disease. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No: CD006974. [DOI: 10.1002/14651858.CD006974.pub2]

Somaraju 2010

Somaraju UR, Tadepalli K. Hematopoietic stem cell transplantation for Gaucher disease. *Cochrane Database of Systematic Reviews* 2010, Issue 7. Art. No: CD006974. [DOI: 10.1002/14651858.CD006974.pub2]

Somaraju 2012

Somaraju UR, Tadepalli K. Hematopoietic stem cell transplantation for Gaucher disease. *Cochrane Database of Systematic Reviews* 2012, Issue 7. Art. No: CD006974. [DOI: 10.1002/14651858.CD006974.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbas 2015	Intervention not relevant, enzyme replacement therapy trial.
Almon 2008	Intervention not relevant, enzyme replacement therapy trial.
Baker 1999	Not an RCT, quasi-RCT or CCT. Outcomes not relevant.
Barranger 1999	Not an RCT, quasi-RCT or CCT. Intervention not relevant.
Charrow 2014	Intervention not relevant, substrate reduction therapy trial.
Cox 2014	Intervention not relevant, eliglustat compared to imiglucerase.
de Fost 2007	Intervention not relevant, enzyme replacement therapy trial.
Elstein 1998	Intervention not relevant, enzyme replacement therapy trial.
Elstein 2001	Intervention not relevant, enzyme replacement therapy trial.
Garcia 2014	Intervention not relevant.
Gonzales 2010	Intervention not relevant, enzyme replacement therapy trial.
Grabowski 1995	Intervention not relevant, enzyme replacement therapy trial.
Kishnani 2009	Intervention not relevant, enzyme replacement therapy trial.
Lukina 2013	Intervention not relevant, eliglustat trial.
Lukina 2016	Intervention not relevant.
Mankoski 2014	Not an RCT, intervention not relevant.
Medrano-Engay 2013	Intervention not relevant.

Study	Reason for exclusion
Mehta 2008	Intervention not relevant, enzyme replacement therapy trial.
Mistry 2013	Intervention not relevant.
Nuzhnyi 2014	Intervention not relevant.
Orchard 2008	Not an RCT, quasi-RCT or CCT.
Schiffmann 2008	Intervention not relevant, miglustat trial.
Turpault 2015	Intervention not relevant.
Weinreb 2008	Intervention not relevant, AT2101 (pharmacological chaperone) therapy trial.
Wenstrup 2004	Intervention not relevant, enzyme replacement therapy trial.
Zimran 2011	Intervention not relevant, enzyme replacement therapy trial.
Zimran 2012	Intervention not relevant.
Zimran 2013	Intervention not relevant.
Zimran 2014	Intervention not relevant.
Zimran 2015	Intervention not relevant.
Zimran 2016a	Intervention not relevant.
Zimran 2016b	Intervention not relevant.

CCT: controlled clinical trial
RCT: randomised controlled trial

APPENDICES

Appendix 1. Clinicaltrials.gov Search Strategy (Date searched 02 March 2017)

Gaucher disease AND Stem cell transplantation

Appendix 2. Genzymeclinicalresearch.com Search Strategy (Date searched 02 March 2017)

Gaucher disease

Appendix 3. WHO International Clinical Trials Registry Platform (Date searched 02 March 2017)

Stem cell transplantation and Gaucher disease

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	Review updated 19 January 2017. No further updates are planned as no new studies are expected in this area.

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 4, 2008

Date	Event	Description
18 September 2017	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorder's Group's Inborn Errors of Metabolism Regiter identified 36 references, none of which were eligible for inclusion in the review.
18 September 2017	New citation required but conclusions have not changed	Minor changes have been made throughout the review.
11 July 2012	Review declared as stable	This review will no longer be regularly updated. Searches will still be undertaken on a two-yearly basis by the Cochrane Cystic Fibrosis & Genetic Disorders Group. If, in future, relevant trials are identified, the review will be updated again.
10 May 2012	New citation required but conclusions have not changed	New searches have been carried out but no changes have been made to the conclusions.
10 May 2012	New search has been performed	A search of the Group's Inborn Errors of Metabolism Register identified three references which have all been listed in Excluded studies (Gonzales 2010; Kishnani 2009; Zimran 2011). New searches of the websites: www.clinicaltrials.gov; www.genzymeclinicalresearch.com, did not identify any trials eligible for inclusion in the review.
4 June 2010	New search has been performed	New searches have been carried out, resulting in no significant changes to the review. Four trials have been added to Excluded studies (Almon 2008; Mehta 2008; Schiffmann 2008; Weinreb 2008).
12 August 2009	Amended	Contact details updated.

Date	Event	Description
7 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

The protocol was conceived and drafted by Usha Somaraju, with inputs from Krishna Tadepalli.

The review drafted by Usha Somaraju, with inputs from Krishna Tadepalli.

Usha Somaraju acts as the guarantor of the review.

DECLARATIONS OF INTEREST

Both authors: none known.

SOURCES OF SUPPORT

Internal sources

- American University of Antigua, College of Medicine, Antigua and Barbuda

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The section of 'Assessment of risk of bias in included studies' has been modified in light of the release of the new RevMan 5.3 software and the publication of the new *Cochrane Handbook for Systematic Review of Interventions 5.3* produced by Cochrane.

INDEX TERMS

Medical Subject Headings (MeSH)

Gaucher Disease [*surgery]; *Hematopoietic Stem Cell Transplantation [mortality]

MeSH check words

Humans