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Enzyme replacement therapy with laronidase (Aldurazyme®) for treating mucopolysaccharidosis type I (Review)

Jameson E, Jones S, Remmington T

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[Intervention Review]

Enzyme replacement therapy with laronidase (Aldurazyme®) for treating mucopolysaccharidosis type I

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ABSTRACT

Background

Mucopolysaccharidosis type I can be classified as three clinical sub-types; Hurler syndrome, Hurler-Scheie syndrome and Scheie syndrome, with the scale of severity being such that Hurler syndrome is the most severe and Scheie syndrome the least severe. It is a rare, autosomal recessive disorder caused by a deficiency of alpha-L-iduronidase. Deficiency of this enzyme results in the accumulation of glycosaminoglycans within the tissues. The clinical manifestations are facial dysmorphism, hepatosplenomegaly, upper airway obstruction, skeletal deformity and cardiomyopathy. If Hurler syndrome is left untreated, death ensues by adolescence. There are more attenuated variants termed Hurler-Scheie or Scheie syndrome, with those affected potentially not presenting until adulthood. Enzyme replacement therapy has been used for a number of years in the treatment of Hurler syndrome, although the current gold standard would be a haemopoietic stem cell transplant in those diagnosed by 2.5 years of age. This is an updated version of the original Cochrane Review published in 2013 and previously updated in 2015.

Objectives

To evaluate the effectiveness and safety of treating mucopolysaccharidosis type I with laronidase enzyme replacement therapy as compared to placebo.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register, MEDLINE via OVID and Embase.

Date of most recent search: 30 January 2019.

Selection criteria

Randomised and quasi-randomised controlled studies of laronidase enzyme replacement therapy compared to placebo.

Data collection and analysis

Two authors independently screened the identified studies. The authors then appraised and extracted data. The quality of the evidence was assessed using GRADE.

Main results

One study (45 participants) met the inclusion criteria. This double-blind, placebo-controlled, randomised, multinational study looked at laronidase at a dose of 0.58 mg/kg/week versus placebo in people with mucopolysaccharidosis type I. All primary outcomes listed in this review were studied in this study. The laronidase group achieved statistically significant improvements in per cent predicted forced vital capacity compared to placebo, MD 5.60 (95% confidence intervals 1.24 to 9.96) (low-quality evidence) and in the six-minute-walk test (mean improvement of 38.1 metres in the laronidase group; P = 0.039, when using a prospectively planned analysis of covariance) (low-quality evidence). The levels of urinary glycoaminoglycans were also significantly reduced (low-quality evidence). In addition, there were improvements in hepatomegaly, sleep apnoea and hypopnoea. Laronidase antibodies were detected in nearly all participants in the treatment group with no apparent clinical effect and titres were reducing by the end of the study (very low-quality evidence). Infusion-related adverse reactions occurred in both groups but all were mild and none necessitated medical intervention or infusion cessation (low-quality evidence). As assessed by questionnaires,changes in a 'Disability Index' after treatment were small and did not differ between groups (low-quality evidence). There were no deaths in either group (low-quality evidence).

Authors' conclusions

The current evidence demonstrates that laronidase is effective when compared to placebo in the treatment of mucopolysaccharidosis type I. The included study was comprehensive, with few participants and of low quality. The study included all of the key outcome measures we wished to look at. It demonstrated that laronidase is efficacious in relation to reducing biochemical parameters (reduced urine glycosaminoglycan excretion) and improved functional capacity as assessed by forced vital capacity and the six-minute-walk test. In addition glycosaminoglycan storage was reduced as ascertained by a reduction in liver volume. Laronidase appeared to be safe and, while antibodies were generated, these titres were reducing by the end of the study. More studies are required to determine long-term effectiveness and safety and to assess the impact upon quality of life. Enzyme replacement therapy with laronidase can be used pre- and peri-haemopoietic stem cell transplant, which is now the gold standard treatment in those individuals diagnosed under 2.5 years of age. We do not anticipate any further trials to be undertaken and therefore do not plan to update this review.

PLAIN LANGUAGE SUMMARY

Enzyme replacement therapy with laronidase as a treatment for mucopolysaccharidosis type I (MPS I)

Review question

We reviewed the evidence about the effect and safety of enzyme replacement therapy with laronidase for people with mucopolysaccharidosis type I (MPS I) who do not undergo haemopoietic stem cell transplantation and in people with MPS I who receive enzyme replacement therapy prior to haemopoietic stem cell transplantation. This is an updated version of the original Cochrane Review published in 2013 and previously updated in 2015.

Background

Hurler syndrome or mucopolysaccharidosis type I is a rare genetic disorder that occurs when an enzyme that the body needs is missing or not working well enough. This leads to the build up of a number of complex molecules in certain cells and tissues. If untreated, this results in a classic picture of dwarfism, enlargement of body organs and a reduction in thinking ability. It occurs when a person inherits two copies of the defective gene (one from each parent) and is just as common in males as in females. It classically presents in infancy, however milder versions can present in adulthood. Enzyme replacement therapy with laronidase aims to replace the missing enzyme; however, given its high cost, it is essential to assess how effective and safe this treatment is.

Search date

The evidence is current to: 30 January 2019.

Study characteristics

One 26-week randomised controlled study (45 participants) was included in the review. Participants were aged between six and 43 years old. The study was carried out in several centres around the world. Participants either received an intravenous infusion of laronidase 0.58 mg/kg or a placebo ('dummy' infusion).

Key results

Current evidence is limited because we only found one randomised clinical trial in the medical literature, which did not include very many participants. Compared with placebo, enzyme replacement therapy improved lung function, the individuals' ability to walk, reduced the excretion of abnormal glycosaminoglycans (a type of carbohydrate molecule) in the urine and also reduced the stopping of breathing related to sleep. Adverse reactions in relation to the infusions occurred in both groups but all were mild and none required medical intervention or for the infusions to be stopped. Enzyme replacement therapy can be used before and around the time of stem cell transplant, which is now the gold standard treatment for Hurler syndrome in individuals diagnosed before the age of two and a half years.

More studies are needed to look at the long-term effects of this treatment and also to see the effects on the quality of life of these individuals. We do not anticipate any further trials to be undertaken and therefore do not plan to update this review.

Quality of the evidence

The included study was small and of low quality.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

Laronidase compared with placebo for mucopolysaccharidosis type I

Patient or population: adults and children with mucopolysaccharidosis I

Settings: outpatient

Intervention: laronidase 0.58 mg / kg given weekly for 26 weeks

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Laronidase				
Change in urinary GAG excretion from baseline Follow-up: 26 weeks	Mean increase of 47.3%	Mean reduction of 54.1%	**N/A**	43 (1)	⊕⊕⊖⊖ **low[1,2]**	<0.001 No standard deviations were given in the paper.
Mean percentage change from baseline in FVC (% predicted) Follow-up: 26 weeks	The mean percentage change in FVC (% predicted) was - 0.7 % (SD 5.9)	The mean percentage change was 5.6% higher (1.2 % higher to 9.96 % higher) in the laronidase group.	N/A	45 (1)	⊕⊕⊖⊖ **low[1,2]**	
Mean change from baseline in 6MWT (metres) Follow-up: 26 weeks	The mean change in 6MWT was -18.4 metres (SD 67.5)	The mean change in 6MWT in the laronidase group was was 38.1 metres higher than the placebo group (1.7 metres lower to 77.9 metres higher)	NA	45 (1)	⊕⊕⊖⊖ **low[1,2]**	Our analysis shows a non significant difference between laronidase and placebo MD 38.10 (95% CI -1.68 to 77.88). The paper reports a significant difference favouring laronidase in a pre-planned ANCOVA that took into account study centre, sex and baseline 6MWT, standing height and liver volume (P = 0.039).
Infusion-related reactions (number of participants with one or more reaction)	**478 per 1000**	**244 per 1000** (72 to 817 per 1000)	**OR**	45 (1)	⊕⊕⊖⊖ **low[1,2]**	

Follow-up: 26 weeks			**0.51** (0.15 to 1.71)			
Antibody production: number of participants developing IgG antibodies Follow-up: 26 weeks	**0 per 1000**	Unable to calculate as assumed risk is zero	**OR** **385.4** (17.47 to 8500.51)	45 (1)	⊕⊖⊖⊖ **very low[1,3]**	In the laronidase group, 91% of patients (20 out of 22) developed IgG antibodies versus none in the placebo group.
Quality of life	Changes in the Disability Index after treatment were "small and did not differ between groups"			45 (1)	⊕⊕⊖⊖ **low[1,2]**	No numerical results presented in the paper.
Mortality: number of deaths Follow-up: 26 weeks	There were no deaths in either group			45 (1)	⊕⊕⊖⊖ **low[1,2]**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
6MWT: six-minute walk test; **CI**: confidence interval; **FVC**: forced vital capacity; **GAG**: glycosaminoglycans; **OR**: odds ratio.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

1. Downgraded once due to an unclear risk of bias within the study from lack of information on process of randomisation and allocation concealment
2. Downgraded once due to imprecision as the study had a small number of participants. There was no explanation of the sample size calculation and whether there were enough participants to show an effect.
3. Downgraded twice due to imprecision as the study number was small and event rates were low.

BACKGROUND

A glossary of terms can be found in the appendices (Appendix 1).

Description of the condition

Mucopolysaccharides, more commonly termed glycosaminoglycans (GAGs), are essential components of connective tissue providing structural support, as well as being involved in cellular regulation and communication. They are sugars composed of highly sulfated, alternating uronic acid and hexosamine residues, assembled into repeating units bound to specific core proteins within complex macromolecules called proteoglycans. Lysosomes are the cell organelles which are involved in the degradation of these large proteoglycans. The process of degradation requires several acid hydrolases. Deficiency of any one of these hydrolases results in a specific disease state. Mucopolysaccharidosis type I (MPS I) results when there is a deficiency of the enzyme alpha-L-iduronidase. This results in the inability of the lysosomes to breakdown two specific GAGs, dermatan sulphate and heparan sulphate.

MPS I is an autosomal recessive disease with an incidence of 1 in 100,000 (Meikle 1999; Neufeld 2001) and is caused by mutations in the gene encoding alpha-L-iduronidase located on chromosome 4p16.3. The pathological MPS I alleles display significant ethnic variation. The common gene mutations in white populations are p.W402X and p.Q70X (Terlato 2003). The disorder can be detected on the screening of urine for urinary GAGs and if this is positive, confirmed by white cell enzyme analysis followed by mutation analysis. It is possible to perform antenatal testing on chorionic villus samples.

Mucopolysaccharidosis type I can be classified as three clinical sub-types; Hurler syndrome, Hurler-Scheie syndrome and Scheie syndrome, with the scale of severity being such that Hurler syndrome is the most severe and Scheie syndrome the least severe. In cases of Hurler syndrome the child classically presents in the first year of life. The presentation can be varied and may take the form of cardiomyopathy, recurrent ear, nose and throat symptoms or recognition of coarse facies. Over the second and third years of life the other classic features of short stature and bony deformity, developmental delay, hepatosplenomegaly and corneal clouding develop. The clinical consequence is a chronic, progressive multi-system disease, which if left untreated results in death by adolescence. At the opposite end of the spectrum, children with Scheie syndrome are intellectually normal and can have a normal life span; however, many will become disabled due to degenerative bony disease, corneal opacity and valvular heart disease. Many cases of MPS I are recorded on the MPS I Registry (MPS I Register 2011). This is a database which contains the clinical, investigation and treatment details of those patients registered. This database provides valuable information which can be used for evidence-based research and practice. Data from the MPS I Registry show that more than half of the study population have Hurler syndrome with a quarter having Hurler-Scheie syndrome and one tenth Scheie syndrome (D'Aco 2012). Biochemically, the different phenotypes are indistinguishable and it is being increasingly acknowledged that MPS I represents a disease spectrum.

Enzyme replacement therapy (ERT) either alone or in combination with haemopoietic stem cell transplantation (HSCT) is the mainstay of treatment. It has been shown that early treatment with ERT corresponds with a better outcome and that the use of HSCT prior to two years of age preserves cognition. In order to therefore maximise outcomes, the diagnosis of MPS I must be made in a timely manner. It is thus postulated that MPS I may be a candidate to be part of an expanded newborn screening schedule. It would be a suitable screening candidate as it can be detected on a blood spot sample, there is an effective treatment available and outcomes are much improved with early diagnosis. There would, however, be cost implications as ERT and HSCT are expensive therapies, and more research would be required into the effectiveness and long-term outcomes.

Description of the intervention

In people with Hurler syndrome, ERT with laronidase, and in recent years laronidase in combination with HSCT in children under two years of age, has become the mainstay of treatment (Muenzer 2009).The latter is the preferred treatment regimen as transplantation provides an endogenous source of the missing enzyme, avoids the need for long-term ERT and is better able to preserve cognition. The children typically receive laronidase between diagnosis and transplantation in order to maximise their pre-transplantation condition and thus reduce their transplantation morbidity and mortality risks. The laronidase is then continued throughout conditioning and until donor engraftment has occurred.

Laronidase (Aldurazyme®, produced by the Genzyme Corporation) is a specific recombinant alpha-L-iduronidase which received Food and Drugs Administration (FDA) approval as long-term treatment for MPS I in 2003. It is a polymorphic variant of the human enzyme, alpha-L-iduronidase, with a molecular weight of 83 kD. It is produced by recombinant DNA technology in a Chinese hamster ovary cell line. The rationale of therapy is to provide exogenous enzyme for uptake into lysosomes and so to increase the catabolism of GAGs, and prevent their build up in tissues. The uptake of laronidase by cells into lysosomes is most likely mediated by the mannose-6-phosphate-terminated oligosaccharide chains of laronidase binding to specific mannose-6-phosphate receptors.

The recommended dose is 0.58 mg/kg administered on a weekly basis as an intravenous infusion. The pharmacodynamic effects have been assessed by analysing alterations in urinary GAG levels; laronidase was shown to significantly reduce these levels. The pharmacokinetics have been evaluated in patients six years and over. The mean plasma clearance ranged from 1.7 to 2.7 ml/min/kg and the mean half life ranged form 1.5 to 3.6 hours (these data come from published information on Aldurazyme® (Genzyme Therapeutics 2010)).

It has been observed that most patients develop antibodies by week 12 of the infusion. Individuals are therefore routinely pre-medicated with antihistamines and anti-pyretics one hour before the infusion commences. Side effects of laronidase include vomiting, nausea, arthralgia, diarrhoea, tachycardia, abdominal pain, hypertension, erythema, and cyanosis. There are no known drug interactions. Overall, the safety data have been encouraging (Clarke 2009).

How the intervention might work

Gaucher disease, another inherited lysosomal storage disorder, is due to a deficiency of the enzyme glucocerebrosidase. The disorder

is characterised by accumulation of the lipid glucocerebroside within the lysosomes of the monocyte-macrophage system and leads to a multi-system disorder with three distinct clinical phenotypes (Charrow 2000). In 1991 targeted ERT in the form of Cerezyme® (imiglucerase for injection) was developed by the Genzyme Corporation in co-operation with the National Institutes of Health (NIH). It was introduced into clinical practice in 1994 and it was seen to alleviate and even reverse many effects of Type 1 Gaucher disease (Weinreb 2002). It was therefore postulated that ERT might also work in MPS I and consequently laronidase was developed using a canine model. Laronidase has subsequently been used in humans to replace the missing alpha-L-iduronidase and so allow the lysosomes to breakdown dermatan sulphate and heparan sulphate.

Why it is important to do this review

Debate has arisen regarding the potential for newborn screening for MPS I, as it is believed that the earlier the condition is diagnosed the better the outcome. The aim of this review is to evaluate the effectiveness of ERT with laronidase for patients with MPS I.

This review is important to conduct because:

- it will be the first systematic review of the use of laronidase in the management of MPS I;
- data collation will allow provision of an evidence-based rationale for management recommendations;
- the systematic review will be of use to the MPS I Registry (MPS I Register 2011);
- it can be used in the debate surrounding newborn screening for MPS I.

This is an update of a previously published version of this Cochrane Review (Jameson 2013). We do not anticipate any further trials to be undertaken and therefore do not plan to update this review.

OBJECTIVES

The objectives of this review are to assess the effectiveness and safety of ERT with laronidase in the management of patients with:

1. MPS I who do not undergo HSCT;
2. MPS I who receive ERT prior to HSCT.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled studies.

Types of participants

We aimed to study two groups of children:

1. children aged 0 to 16 years with MPS I who receive only laronidase and do not undergo HSCT;
2. children aged 0 to 16 years with MPS I who receive laronidase prior to undergoing HSCT.

For future updates, if a study has a population of children from both the above two groups, authors will be contacted for individual data. These data will then be incorporated into the appropriate subgroups. The diagnosis in these children will have been established by accepted criteria of mutation analysis and enzyme concentration.

Types of interventions

Two intervention strategies compared to placebo:

1. ERT with laronidase given for a period of at least one month when HSCT is not performed;
2. ERT with laronidase given for a period of at least one month prior to HSCT.

Types of outcome measures

Primary outcomes

1. Glycosaminoglycan (GAG) levels in urine
2. Respiratory function as assessed by pulmonary function tests (e.g. forced expiratory volume at one second (FEV_1), force vital capacity (FVC))
3. Endurance performance as assessed by endurance test in the form of the six-minute walk test (6MWT)

Secondary outcomes

1. Adverse effects of treatment, particularly incidence of allergic reactions to laronidase, increase in antibody titres and problems delivering the therapy
2. Antibody production
3. Echocardiographic findings (measures of systolic and diastolic function, hypertrophy and valve disease)
4. Height
5. Improvement in symptoms of nocturnal hypoventilation and sleep apnoea
6. Quality of life
7. Mortality
8. Effects on cognition (based on standard psychometric testing appropriate to age)
9. Liver volume*

* Post hoc change: this outcome has been added given that it demonstrates the reduction in GAG storage in the liver and is used clinically to check for recurrence of hepatomegaly if concerns are raised regarding the effectiveness of treatment.

Search methods for identification of studies

Electronic searches

Relevant studies were identified by searching the Inborn Errors of Metabolism Trials Register using the term: mucopolysaccharidosis.

The Coagulopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE and the prospective handsearching of one journal - *Haemophilia*. Unpublished work is identified by searching the abstract books of major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Congress of the World Federation of Hemophilia; the European Association for Haemophilia and Allied Disorders, the American Society of Gene and Cell Therapy and

the International Society on Thrombosis and Haemostasis. 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 most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register: 30 January 2019.

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: 01 October 2018.

We also searched Embase and MEDLINE via OVID. For the full search strategies, please refer to the relevant appendix (Appendix 3). No limitation was placed on the years searched. Date of the most recent search: 27 December 2015.

Searching other resources

The reference lists of identified studies were reviewed with an aim to identify further studies not highlighted by the searches.

Data collection and analysis

Selection of studies

Two authors (SJ and EJ) independently assessed the titles and abstracts of the citations identified by the search strategy in order to select studies that fitted the inclusion criteria. There were no disagreements on selection.

Data extraction and management

Two authors (SJ and EJ) independently extracted data. There were no discrepancies or differences. The authors used a standard form to extract the following information: characteristics of the study; participants; interventions; and outcomes. The protocol had stated that outcomes would be assessed according to:

1. those who had received ERT prior to HSCT and those who did not receive HSCT;
2. those with central nervous system disease and those without;
3. outcomes at selected time periods.

We only identified one study and it did not cover these three subgroups. We report data from this study at 26 weeks of treatment. Analysis was undertaken using RevMan 5 (RevMan 2011).

Assessment of risk of bias in included studies

Two authors (EJ, SJ) assessed the risk of bias independently using the tool documented in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 20011a). We assessed the following domains as having either a low, high, or unclear 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;
6. other sources of bias.

We have displayed the results of the risk of bias assessment in the 'Risk of bias' table in the section 'Characteristics of included studies' (Characteristics of included studies).

Measures of treatment effect

The authors calculated the pooled estimates of treatment effects across the included studies using pooled odds ratio (OR) for dichotomous data and pooled mean differences (MDs) for continuous data and the corresponding 95% confidence intervals (CIs). This would then have allowed calculation of the numbers needed to treat (NNT) and their 95% CIs from the pooled OR and its 95% CI for a specific baseline risk, which is the sum of all the events in the control groups (in all studies) divided by the total participant numbers in control groups in all studies (using an online calculator (Cates 2003)). However, this was not possible due to the small numbers of participants.

As per our protocol, we were able to present data at one of our pre-specified time-periods, i.e. at six months. For future updates, if we are able to include more studies, we plan to group outcomes into the following time periods, e.g. at six months, at one year, at five years, at 10 years.

Dealing with missing data

The authors reported dropout rates in the 'Characteristics of included studies' table (Characteristics of included studies).

Assessment of heterogeneity

We were only able to include one study and therefore we did not evaluate heterogeneity. If we are able to include further studies when we update this review, we will calculate inconsistencies based on the I^2 statistic. This describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error (Higgins 2003). We will interpret the I^2 statistic based on the guidance for thresholds outlined in the *Cochrane Handbook for Systematic Reviews of Interventions.* This means that we will regard below 50% as low heterogeneity, between 50% and 75% as moderate heterogeneity and over 75% as substantial heterogeneity (Higgins 2011b).

Assessment of reporting biases

If we identify further studies for future updates of this review, such that there are at least 10 included studies, we will ascertain publication bias using a funnel plot. An asymmetrical funnel plot, will lead to an exploration for alternative causes in addition to publication bias.

Data synthesis

Qualitative

The authors produced qualitative information relative to methods, risk of bias, description of participants and outcome measures and have documented this information in the table of 'Characteristics of included studies' (Characteristics of included studies).

Quantative

The authors analysed dichotomous variables using the OR and 95% CIs and continuous variables using the MD and 95% CIs.

If we identify any additional studies in future updates, we will incorporate these using either a fixed-effect model in the absence of

moderate or substantial heterogeneity, or a random-effects model if we identify moderate or substantial heterogeneity as described above.

Subgroup analysis and investigation of heterogeneity

We stated in the protocol that outcomes would be assessed according to:

1. those who had received ERT prior to HSCT and those who did not receive HSCT;
2. those with central nervous system disease and those without;
3. outcomes at selected time periods.

However, given there was only one eligible study (which did not make these differentiations), we were not able to carry out any such subgroup analyses.

Sensitivity analysis

We only included one study in the review, so we did not perform any sensitivity analysis. However, if in future updates there are sufficient comparable studies to allow, we plan to perform a sensitivity analysis excluding those studies with a high risk of bias for allocation concealment.

Summary of findings tables and quality of the evidence (GRADE)

In a post hoc change in line with current Cochrane guidance, at the 2019 update we added a summary of findings table for each comparison presented in the review (Summary of findings 1). We selected the following outcomes to report (chosen based on relevance to clinicians and consumers).

1. Glycosaminoglycan (GAG) levels in urine
2. Respiratory function as assessed by pulmonary function tests (e.g. forced expiratory volume at one second (FEV_1), force vital capacity (FVC))
3. Endurance performance as assessed by endurance test in the form of the six-minute walk test (6MWT)
4. Adverse effects of treatment, particularly incidence of allergic reactions to laronidase, increase in antibody titres and problems delivering the therapy
5. Antibody production
6. Quality of life
7. Mortality

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We downgraded evidence by one level if they considered the limitation to be serious and by two levels if very serious.

RESULTS

Description of studies

Results of the search

There were 204 records identified by all of the searches:

- MEDLINE (via OVID): 154 references;
- Cochrane Cystic Fibrosis and Genetic Disorders Group's Trials Register: 29 references;
- Embase: 0 references.
- ClinicalTrials.gov and the WHO ICTRP: 21 references .

The authors reviewed the titles and abstracts. Five duplicates were removed, a total of 180 references were excluded based on title alone. A further 19 references were regarded as potentially relevant and were selected for further review. Of those selected, the bibliographical references were reviewed looking for further potentially eligible studies, but none were found. After further review of these 11 studies (19 references), nine were excluded from further analysis. Full text copies of the two remaining studies (10 references) were obtained and were then subjected to further assessment. Following the verification of two whole studies, only one (six references) fulfilled all the inclusion criteria of this review (Wraith 2004) and one (four references) was excluded (Giugliani 2008). Thus, one study (six references) was included and 10 studies (13 references) were excluded (see 'Excluded studies' section).

Included studies

The included study was a multicentre, multinational, double-blind, randomised, placebo-controlled, 26-week, phase III study of the efficacy and safety of laronidase 0.58 mg/kg (100 units/kg) administered weekly in patients with MPS I (Wraith 2004).

Participants

The study included 45 patients with MPS I. The biochemical evidence of MPS I was a documented deficiency of iduronidase activity of less than 10% of normal in addition to measurable clinical disease. Included patients had to be at least five years old, be able to perform a reproducible FVC manoeuvre that was less than or equal to 80% of normal based on the Polgar formula, be able to stand independently and be able to walk a minimum of five metres in six minutes. Exclusion criteria were a previous tracheostomy or bone marrow transplant; pregnancy or lactation; administration of any investigational drug within 30 days before enrolment; a medical condition or other circumstance that could interfere with compliance or a known hypersensitivity to laronidase, components of laronidase or the placebo solution. The mean age of the patients in the laronidase arm was 15.6 years (range 7 to 43 years) and in the placebo arm 15.4 years (range 6 to 39 years). The laronidase group consisted of 11 males and 11 females; the placebo group 11 males and 12 females.

Interventions

The 45 patients were randomly assigned to either weekly intravenous laronidase 100 U/kg (0.58 mg/kg) in a solution of sodium phosphate, sodium chloride and polysorbate-80 or to the same solution but without the laronidase. All treatments were diluted in 0.1% human albumin in normal saline and given over four hours. All patients were pre-medicated with an anti-pyretic and an antihistamine.

Outcomes

The primary efficacy outcomes of the one included study compared the median change from baseline to week 26 between the treatment and placebo groups in percentage of predicted normal FVC and in a 6MWT distance. The FVC measurements were obtained

by spirometry in accordance with the American Thoracic Society guidelines (ATS 1995). The secondary outcomes were: adverse events; antibody production; nocturnal hypoventilation and sleep apnoea; quality of life; and mortality. Again, results were presented as change from baseline.

Excluded studies

A total of 10 studies were excluded (Chen 2015; de Rue 2011; Giugliani 2008; Grewal 2005; Kakkis 2001a; Kakkis 2001b; Pitz 2007; Salehpour 2015; Wraith 2007; Wynn 2008). One study was a phase I study with no placebo arm (Kakkis 2001a); one was a consensus report (de Rue 2011); two were on intrathecal ERT (Chen 2015; Salehpour 2015), one was concerned with dose optimisation (Giugliani 2008); one was concerned with safety, pharmacokinetics and efficacy (Wraith 2007); one was an overview of ERT (Kakkis 2001b); and one because it did not cover the described outcomes, only commenting on an ophthalmology outcome (Pitz 2007). A further two were excluded because they were narrative reviews of the effects of laronidase prior to bone marrow transplant (Grewal 2005; Wynn 2008). For further information, please refer to the 'Characteristics of excluded studies' table (Characteristics of excluded studies).

Risk of bias in included studies

Allocation

Generation of the randomisation sequence

Generation of the randomisation sequence was not clearly described in the included study and therefore assessed as having an unclear risk of bias (Wraith 2004).

Allocation concealment

Likewise, allocation concealment was not discussed in the study, which is also categorised as having an unclear risk of bias (Wraith 2004).

Blinding

The study was double-blinded, and all patients received weekly intravenous infusions (Wraith 2004). The primary outcome assessments were conducted by the responsible medical teams. We therefore judged the study to have a low risk of bias for blinding of participants, clinicians and outcome assessors.

Incomplete outcome data

All participants completed the study (Wraith 2004). There were no deaths. We have therefore assessed this domain as having a low risk of bias.

Selective reporting

All important clinical outcomes were evaluated (Wraith 2004). We therefore assessed this domain as having a low risk of bias.

Other potential sources of bias

We believe that the study was free of other problems that could put it at a high risk of bias (Wraith 2004).

Effects of interventions

See: **Summary of findings 1** Summary of findings

In the included study, patients were randomised into two groups; laronidase 0.58 mg/kg (100 IU/Kg) weekly or placebo weekly (Wraith 2004).

The quality of the evidence has been graded for those outcomes included in the summary of findings table. For the definitions of these gradings, please refer to the summary of findings tables (Summary of findings 1).

Primary outcomes

1. Glycosaminoglycan levels in urine

Urinary GAG excretion rapidly and significantly decreased in the laronidase group (Wraith 2004). By week 26 the laronidase group showed a mean reduction of 54.1% in urinary GAG excretion compared to a mean increase of 47.3% in the placebo group (P = < 0.001) (low-quality evidence) (Analysis 1.1); standard deviations (SDs) were not included in the paper. In the treatment group, mean reduction to levels approaching the upper limit of normal occurred by week four and were maintained throughout treatment.

2. Respiratory function

After 26 weeks of treatment patients receiving laronidase showed a mean 5.6 percentage point increase in per cent of predicted normal FVC compared with the placebo group (median 3.0; P = 0.009), MD 5.60 (95% CI 1.24 to 9.96) (low-quality evidence) (Analysis 1.2). The improvement remained significant when per cent of predicted normal FVC was calculated by using each patient's current rather than baseline height (mean 4.3 and median 22 percentage point difference, P = 0.022). The treatment effect was maintained (P = 0.007) when study centre and baseline FVC, apnoea-hypopnoea index (AHI), total lung capacity, liver volume and urinary GAG level were taken into account by an analysis of covariance (ANCOVA).

3. Endurance performance as assessed by 6MWT

After 26 weeks treatment the laronidase group showed a mean 38.1 metre increase in 6MWT compared with the placebo group (median 38.5, P = 0.066). When the data where entered into the meta-analysis, there was no significant difference observed between the laronidase and the placebo groups, MD 38.10 (95% CI -1.68 to 77.88) (low-quality evidence) (Analysis 1.3). However, the effect achieves statistical significance (P = 0.039) in a prospectively planned ANCOVA that took into account study centre, sex and baseline 6MWT, standing height and liver volume. The original paper reports that 6MWT was higher in the laronidase group at each time point compared to placebo (means only estimable on a graph and no SDs provided).

Secondary outcomes

1. Adverse effects of treatment, particularly incidence of allergic reactions to laronidase, increase in antibody titres and problems delivering the therapy

Except for one patient in the laronidase group, all patients had at least one adverse event, the majority being associated with the underlying MPS I. Infusion-related reactions consisting mainly of flushing, fever, headache and rash had a similar incidence in both groups, 32% versus 48% in the laronidase versus placebo groups respectively. Most were mild and none required medical intervention or interruption of infusions, there was no significant difference between the laronidase and the placebo groups, OR 0.51 (95% CI 0.15 to 1.71) (low-quality evidence) (Analysis 1.4).

2. Antibody production

In the laronidase group, 91% of patients (20 out of 22) developed IgG antibodies. Mean (SD) time to seroconversion was 52.6 (24.1) days (range 20 to 106). By study end, most antibody levels were declining (very low-quality evidence).

3. Echocardiographic findings

No measures of systolic and diastolic function, hypertrophy and valve disease were reported on in the included study (Wraith 2004).

4. Height

This outcome was not reported on in the included study (Wraith 2004).

5. Improvement in symptoms of nocturnal hypoventilation and sleep apnoea

After 26 weeks treatment the mean AHI decreased by 3.6 events per hour in the laronidase group compared with the placebo group (P = 0.145). Since nearly half the group had normal baseline sleep studies, a *post hoc* subgroup analysis was performed on patients whose baseline AHI suggested sleep apnoea. This showed that the laronidase group (n = 10) had a mean decrease of six events per hour of sleep during the study compared to the placebo group (n = 9) who had a mean increase of 0.3 events per hour. The 11.4 events per hour treatment benefit (between group difference in adjusted mean changes calculated using the ANOVA model) was significant at P = 0.014. Relevant data were not available to allow us to produce a meta-analysis.

6. Quality of life

The study investigators reported that for the 'Childhood Health Assessment Questionnaire' (CHAQ) and 'Health Assessment Questionnaire' (HAQ) at baseline the "Disability Index scores were 1.9 for the placebo group and 2.0 for the laronidase group (scale of 0 to 3, with 3 the most disabled) (Wraith 2004). Changes in the Disability Index after treatment were "small and did not differ between groups" (low-quality evidence).

7. Mortality

There were no deaths in either group (low-quality evidence) (Wraith 2004).

8. Effects on cognition

This outcome, based on standard age-appropriate psychometric testing was not reported in the included study (Wraith 2004).

9. Liver volume

Mean liver volume was used as a marker of storage material. In the laronidase group, 13 out of 18 (72%) participants with abnormal liver volumes at baseline attained normal volumes at week 26 versus 3 out of 14 (21%) in the placebo group. Overall, there was a significant difference in favour of the laronidase group, with mean liver volume decreasing by 18.9% in the laronidase group and increasing by 1.3% in the placebo group, MD 20.00 (95%CI 8.93 to 31.07) (Analysis 1.6).

DISCUSSION

Summary of main results

The first use of enzyme replacement therapy (ERT) in mucopolysaccharidosis type I (MPS I) was described by Kakkis in 10 MPS I patients aged five to 22 years treated with recombinant human α-L-iduronidase for 52 weeks (Kakkis 2001a). This demonstrated clinical and biochemical improvement, and led to the 26-week, randomised, placebo-controlled study included in this review (Wraith 2004). This study demonstrated statistically significant benefits in the primary outcomes of this review, i.e. level of urinary glycosaminoglycans (GAGs), respiratory function in the form of forced vital capacity (FVC) and endurance as measured by the six-minute walk test (6MWT). In addition, there was improvement in mean liver volume and symptoms of sleep hypoventilation and apnoea. Laronidase was generally well-tolerated with reported adverse effects being predominantly infusion related. No severe adverse events were reported. The majority of patients developed IgG antibodies, but these levels were declining in the majority of patients by the end of the study.

Overall completeness and applicability of evidence

The included study provided data on the short-term efficacy and safety of laronidase in patients aged six to 43 years. The positive results seen in this study were reflected in the subsequent open-label extension study (Clarke 2009). The introduction of haemopoietic stem cell therapy has revolutionised the treatment of MPS I and should be the gold standard for treating Hurler syndrome.

Quality of the evidence

One study fulfilled the inclusion criteria and had a very small number of participants and was of low quality. In relation to the risk of bias, the main limitation was the lack of information with regards to allocation generation and concealment.

Potential biases in the review process

There are no obvious potential biases. All conflicting interests are declared.

Agreements and disagreements with other studies or reviews

The 45 participants included in the study were subsequently enrolled into a 3.5 year extension study (Clarke 2009). This demonstrated long-term clinical benefit with continued improvement in FVC, the 6MWT, sleep symptoms, shoulder flexion and '(Childhood Health Assessment Questionnaire' (CHAQ) and 'Health Assessment Questionnaire' (HAQ) scores. Laronidase continued to be well-tolerated with infusion reactions being easily managed and the number of these decreasing after six months. One individual experienced an anaphylactic reaction and one patient died, but this was due to an unrelated treatment for an upper respiratory tract infection. Antibodies developed in 93% of participants, but 29% were seronegative at their last assessment.

A large number of individuals are diagnosed at under five years of age and so would potentially benefit from ERT. As the first study did not include children aged under five years, a 52-week, prospective, open-label, multinational study of 20 children with MPS I under five years of age was conducted (Wraith 2007). This demonstrated its

safety and efficacy in this age group at a dose of 0.58 mg/kg per week.

Giugliani conducted a 26-week, randomised, open-label, multinational study comparing three alternative regimens against the standard dose (Giugliani 2008). The alternative dosing regimens were 1.2 mg/kg every two weeks, 1.2 mg/kg every week and 1.8 mg/kg every two weeks among 33 MPS I patients. The outcomes were no further reduction in urinary GAG excretion or liver volume when compared to standard dose. The safety profile at all doses was acceptable with infusion reactions occurring across all regimens, but the lowest number being in the approved dose group (35% versus 25% to 63%). There was one non-treatment related death attributable to acute bronchitis. It was concluded that a dose of 0.58 mg/kg/week provided the best benefit-to-risk ratio with near-maximal reductions in GAGs. The 1.2 mg/kg dose given every two weeks was deemed to be an acceptable alternative for those with difficulty receiving weekly infusions, but the long-term effects are unknown.

While ERT is the mainstay of treatment in the majority of MPS disorders, haemopoietic stem cell transplantation (HSCT) is the gold standard treatment in severe MPS I patients diagnosed under 2.5 years of age. There is a juxtaposition of the two therapies with a recent European consensus review (de Rue 2011) reaching full consensus on several important issues:

1. HSCT is the preferred treatment for those diagnosed before 2.5 years of age with Hurler syndrome;
2. HSCT should be considered in those with an intermediate phenotype if there is a suitable donor though there is no data on efficacy in this group;
3. MPS I patients who have not been transplanted or those whose grafts fail may benefit from ERT;
4. ERT should be started at diagnosis and may be of value in patients awaiting HSCT to optimise pre-transplant fitness.

AUTHORS' CONCLUSIONS

Implications for practice

The randomised clinical study reviewed was of low quality and described all primary outcomes stated in the protocol and the majority of stated secondary outcomes. It has demonstrated that ERT with laronidase is effective in relation to functional capacity and efficacious in terms of liver volumes and urine GAG excretion in patients with MPS I when compared with placebo. It has also been demonstrated to be safe. However, HSCT should be the gold standard for those diagnosed with severe MPS I in the first 2 to 2.5 years of life. Although, ERT with laronidase can be useful for pre-transplantation optimisation and in those with more attenuated disease. There does, however, remain uncertainty about the longer-term outcomes of this lifelong and life-limiting disease and studies looking at quality of life should be undertaken.

Implications for research

It is clear that ERT with laronidase is effective. Longitunidal reviews are now required to study the long-term effects of laronidase and the effects in those patients commenced on treatment either earlier or later in life. The MPS I registry may prove a useful source of data but formal studies will be challenging to implement. In addition to gathering further data regarding long-term outcomes, further research must also take place in regard to the effects of immunogenicity and the clinical consequences when significant antibody titres develop.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Wraith 2004

Study characteristics	
Methods	Multicentre, multinational, double-blind, randomised, placebo-controlled, 26 week clinical study. This was a parallel study with 22 participants in the laronidase group and 23 in the placebo group.
Participants	Patients between the ages of 6 - 43 years with a diagnosis of MPS I based on both clinical and biochemical criteria. Clinical criteria included: patients had to be at least 5 years old, able to perform a reproducible FVC that was less than or equal to 80% predicted, able to stand independently and walk a minimum of 5 metres in 6 minutes. Biochemically they had to have iduronidase activity < 10% of normal as measured in fibroblasts or leukocytes. Patients were excluded based on prior tracheostomy or bone marrow transplantation, pregnancy or lactation, administration of an investigational drug within 30 days before study enrolment, any condition which may affect compliance or known hypersensitivity to laronidase or components of the laronidase or placebo solutions.
Interventions	Intravenous infusions of laronidase 0.58 mg/kg or placebo weekly for 26 weeks.
Outcomes	Primary efficacy outcomes were change from baseline to 26 weeks in terms of FVC and 6MWT. These measures both reflecting endurance capacity. Secondary outcome measures were adverse events, antibody production, improvement in nocturnal hypoventilation and apnoea, quality of life and mortality.
Notes	Data from the extension study are not included in the review.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided about generation of randomisation sequence. Patients randomised equally to 1 of 2 arms.
Allocation concealment (selection bias)	Unclear risk	No information provided in the paper.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study.
Selective reporting (reporting bias)	Low risk	No concerns.
Other bias	Low risk	No other sources of bias identified.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients were blinded. Unclear regarding personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if assessors were blinded.

FVC: forced vital capacity
6MWT: 6-minute walk test

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

Study	Reason for exclusion
Chen 2015	Intrathecal ERT.
de Rue 2011	A consensus report.
Giugliani 2008	Dose optimisation study.
Grewal 2005	Narrative review of ERT and HSCT.
Kakkis 2001a	Phase I/II clinical study evaluating safety and dosing requirements in 10 patients.
Kakkis 2001b	Overview of ERT.
Pitz 2007	Narrative review only concerned with ocular outcome.
Salehpour 2015	Intrathecal ERT.
Wraith 2007	Study to evaluate safety, pharmacokinetics and efficacy.
Wynn 2008	Narrative review of ERT and HSCT.

ERT: enzyme replacement therapy
HSCT: haemopoietic stem cell transplantation

DATA AND ANALYSES

Comparison 1. Laronidase versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in urinary GAG excretion	1		Other data	No numeric data
1.2 Change from baseline in FVC (% of predicted normal)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.1 At week 26	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3 Change from baseline in 6MWT	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 At week 26	1	45	Mean Difference (IV, Fixed, 95% CI)	38.10 [-1.68, 77.88]
1.4 One or more infusion related reactions	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Antibody production	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6 % change in liver volume	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.1 At week 26	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

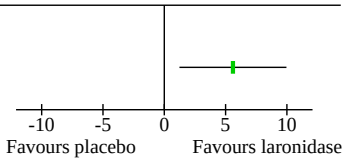
Analysis 1.1. Comparison 1: Laronidase versus placebo, Outcome 1: Change in urinary GAG excretion

Change in urinary GAG excretion

Study	Urinary GAG excretion in laronidase group (n = 21)	Urinary GAG excretion in placebo group (n = 22)	P-value
Wraith 2004	Mean reduction of 54.1%	Mean increase of 47.3%	<0.001

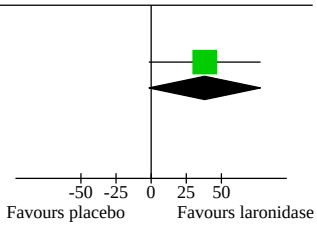
Analysis 1.2. Comparison 1: Laronidase versus placebo, Outcome 2: Change from baseline in FVC (% of predicted normal)

Study or Subgroup	Laronidase Mean	Laronidase SD	Laronidase Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
1.2.1 At week 26							
Wraith 2004	4.9	8.7	22	-0.7	5.9	23	5.60 [1.24 , 9.96]

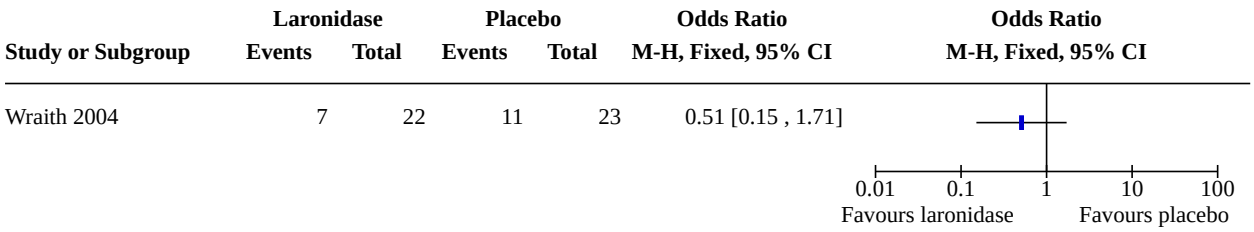


Analysis 1.3. Comparison 1: Laronidase versus placebo, Outcome 3: Change from baseline in 6MWT

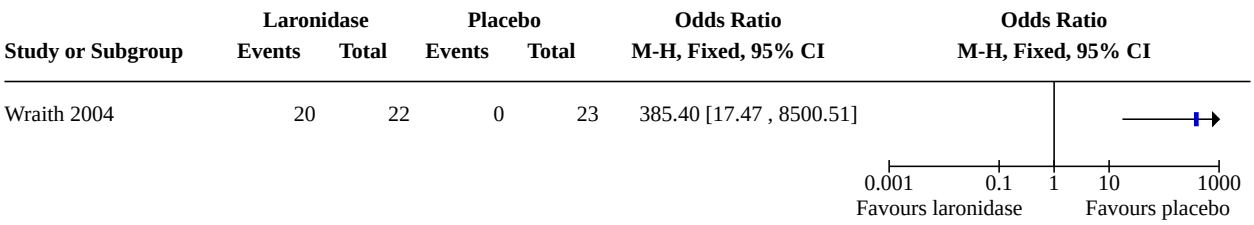
Study or Subgroup	Laronidase Mean	Laronidase SD	Laronidase Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 At week 26								
Wraith 2004	19.7	68.6	22	-18.4	67.5	23	100.0%	38.10 [-1.68 , 77.88]
Subtotal (95% CI)			**22**			**23**	**100.0%**	**38.10 [-1.68 , 77.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.88 (P = 0.06)								



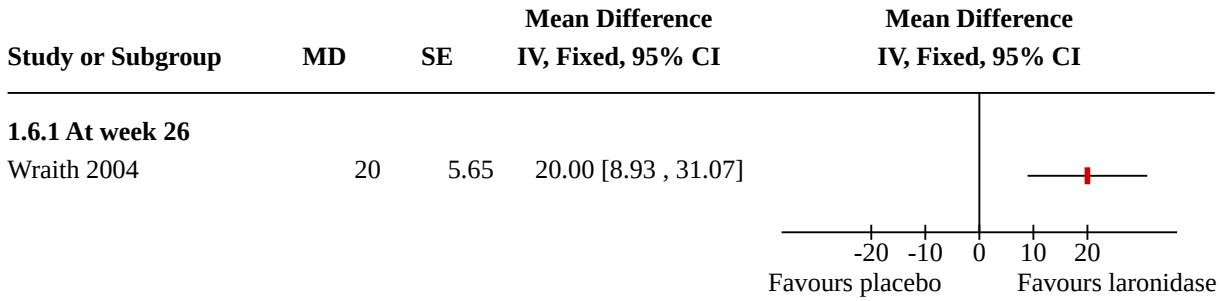
Analysis 1.4. Comparison 1: Laronidase versus placebo, Outcome 4: One or more infusion related reactions



Analysis 1.5. Comparison 1: Laronidase versus placebo, Outcome 5: Antibody production



Analysis 1.6. Comparison 1: Laronidase versus placebo, Outcome 6: % change in liver volume



APPENDICES

Appendix 1. Glossary of terms

Term	Explanation
Dermatan sulphate	A glycosaminoglycan (15 - 40 kD) found mostly in skin, but also in blood vessels, heart valves, tendons, and lungs. It is broken down by L iduronidase, but accumulates intra lysosomally in Hurler syndrome and Hunter syndrome.
Facies	Distinctive facial expressions associated with specific medical conditions.
Gaucher disease	A chronic congenital, autosomal recessive disease of lipid metabolism caused by a deficiency of the beta-glucocerebrosidase enzyme. Clinical features are hepatosplenomegaly (enlargement of liver and spleen) and in severe early onset forms of the disease, with neurological dysfunction.

(Continued)

Glycosaminoglycans	Previously referred to as mucopolysaccharides, are long unbranched polysaccharides consisting of a repeating disaccharide unit. The repeating unit consists of a hexose (six-carbon sugar) or a hexuronic acid, linked to a hexosamine (six-carbon sugar containing nitrogen).
Heparan sulphate	A linear polysaccharide found in all animal tissues. It regulates a wide variety of biological activities, including developmental processes, angiogenesis, blood coagulation and tumour metastasis.
Lysosome	A membrane bounded cytoplasmic organelle containing a variety of hydrolytic enzymes.
Mucopolysaccharidosis	Any of a group of lysosomal storage diseases that have in common a disorder in metabolism of mucopolysaccharides. They are identified by the excretion of various mucopolysaccharides in urine and infiltration of these substances into connective tissue, with resulting various defects of bone, cartilage, and connective tissue.
Pharmacodynamics	The study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure.
Pharmocokinetics	The study of the action of the body on drugs over a period of time, including the processes of absorption, distribution, metabolism, localisation in tissues, biotransformation, elimination and excretion.
Recombinant DNA	Spliced DNA formed from two or more different sources that have been cleaved by restriction enzymes and joined by ligases.

Appendix 2. Search strategies - trial registries

Registry	Search terms
ClinicalTrials.gov	Search terms: enzyme replacement therapy OR laronidase OR Aldurazyme AND randomised Study type: Interventional Studies Condition: Mucopolysaccharidosis I OR hurler OR MPS I Phase: 3
WHO ICTRP	Condition: Mucopolysaccharidosis I OR hurler OR MPS I Intervention: enzyme replacement therapy OR laronidase OR Aldurazyme Recruitment status: ALL

Appendix 3. Search strategies - databases

Database	Search terms
MEDLINE via OVID	No limitations applied. Keywords used: #1 Mucopolysaccharidosis I #2 MPS I

(Continued)

	#3Hurler syndrome #4 Hurler disease #5 Hurler's #6 Hurler #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #8 enzyme replacement therapy #9 ERT #10 laronidase #11 Aldurazyme #12 #8 OR #9 OR #10 OR #11 #13 #7 AND #12
Embase via OVID	No limitations applied. Keywords used: #1 Mucopolysaccharidosis I #2 MPS I #3Hurler syndrome #4 Hurler disease #5 Hurler's #6 Hurler #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 #8 enzyme replacement therapy #9 ERT #10 laronidase #11 Aldurazyme #12 #8 OR #9 OR #10 OR #11 #13 #7 AND #12

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	A search for relevant studies was undertaken on 30 January 2019, all relevant references have been incorporated into the review. This is not an active area of research and no new studies are expected in this area, therefore, we do not plan on updating this review.

HISTORY

Protocol first published: Issue 10, 2011
Review first published: Issue 9, 2013

Date	Event	Description
18 June 2019	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register identified 16 potentially relevant references. A total of 14 references were excluded on title alone and one was an additional reference to the included study (Wraith 2004) and one to an excluded study (Chen 2015). An additional 21 references were identified by a search of clinical trials registries and these were discarded as not relevant. A new summary of findings table has been added to the review and findings from this incorporated into all relevant sections.
18 June 2019	New citation required but conclusions have not changed	The review was updated throughout. Minor changes have been made. Given that there are unlikely to be any trials published in this area, this review will no longer be regularly updated.
5 January 2016	New citation required but conclusions have not changed	Minor changes have been made throughout the review for this update. The 'Plain language summary' was updated in line with the most recent guidelines.
5 January 2016	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Inborn Errors of Metabolism Trials Register identified 35 references. A total of 30 references were disregarded as they were not relevant to the review. Two were additional references to an included study but included data only on a non-randomised extension phase of the study (data not included in the review) (Wraith 2004). One was an overview of enzyme replacement therapy (Kakkis 2001b); two were on intrathecal enzyme replacement therapy (Chen 2015; Salehpour 2015).
20 November 2013	New citation required but conclusions have not changed	A P value has been corrected in the abstract section of the review.
20 November 2013	Amended	An amendment has been made to the abstract.

CONTRIBUTIONS OF AUTHORS

Original review: Dr Elisabeth Jameson wrote the review. Professor James Wraith (deceased, April 2013) and Dr Simon Jones were instrumental in editing and revising the document.

2016 updated review: Dr Elisabeth Jameson led on the update of this review, with input from Dr Simon Jones and Tracey Remmington.

DECLARATIONS OF INTEREST

Dr Elisabeth Jameson: none known.

Dr Simon Jones: received speaking and consultancy fees from both Sanofi and Biomarin, along with travel assistance to conferences.

Tracey Remmington: none known.

SOURCES OF SUPPORT

Internal sources

- No source of internal support identified for this project which will be conducted within the current roles of the author group., Other

External sources

- National Institute for Health Research, UK

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The stated objectives of the protocol were to assess the effectiveness and safety of ERT with laronidase in the following patient groups:

1. those who had received ERT prior to HSCT and those who did not receive HSCT;
2. those with central nervous system disease and those without;
3. outcomes at selected time periods.

As only one study was identified and it did not cover these three subgroups it was only possible to report data at 26 weeks of treatment. This the review has therefore merely focused upon the use of laronidase in the treatment of MPS I.

Secondary outcome: 9. Liver volume. This outcome has been added given that it demonstrates the reduction in GAG storage in the liver and is used clinically to check for recurrence of hepatomegaly if concerns are raised regarding the effectiveness of treatment.

INDEX TERMS

Medical Subject Headings (MeSH)

*Enzyme Replacement Therapy [methods]; *Iduronidase [therapeutic use]; *Mucopolysaccharidosis I [drug therapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Humans