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Enzyme replacement therapy for mucopolysaccharidosis type IV (Morquio syndrome) (Protocol)

Shemesh E, Deroma L, Hendriksz CJ, Hollak C, Krishan A

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[Intervention Protocol]

Enzyme replacement therapy for mucopolysaccharidosis type IV (Morquio syndrome)

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

1. To assess the effectiveness, safety and appropriate dose regimen of ERT in people with MPS IV A.

2. To determine whether evidence from NRSIs (which potentially offers longer follow-ups) can contribute to the ERT efficacy evidence-base, and to determine the potential need for additional RCT evidence.

3. To consolidate recommendations for the design of future clinical trials.

BACKGROUND

Please refer to the glossary of terms (Appendix 1).

Description of the condition

Mucopolysacharidoses (MPS) are a group of lysosomal storage disorders (LSDs) which are characterized by the accumulation of extracellular macromolecules named glycosaminoglycans (GAGs). These macromolecules have structural significance in the building of connective tissue and cartilage, and are also important agents for the regulation of diverse biochemical cascades, such as coagulation, immune response and pathogen recognition and removal (the complement system), inter-cellular communications and wound healing (Linhardt 2004). Given their complex structure, several enzymes are needed for the complete lysosomal breakdown of these macromolecules. Deficiency in any of the enzymes leads to the accumulation of GAGs in high concentrations, mainly inside chondrocytes and in the extracellular matrix, leading to inflammation and apoptosis (cell death). Morquio syndrome is one of the seven known phenotypes of MPS, classified into two types based on the enzymatic deficiency: type IV A galacosamine 6 sulfa-

tase (GALNS) deficiency (Morrone 2014) (OMIM #253000) and type IV B beta galactosidase deficiency (Bonafe 2015) (OMIM #253010), both resulting in a defective catabolic process of keratan sulfate (KS). The reduced capacity to fully degrade KS results in its accumulation within the skeletal system, visceral organs, heart valves and the eyes (Yasuda 2013). This review will focus on MPS IV A. Prominent features of MPS IV A are skeletal dysplasia (short stature, pectus carinatum, kyphosis, joint abnormalities, odontoid hypoplasia) (Di 2012), hepatomegaly (enlarged liver) (Montano 2007), anomalies of the teeth (James 2012), corneal clouding (Montano 2007), hearing difficulties (Harmatz 2013) and heart valve defects (Hendriksz 2013a).

Description of the intervention

The concept of enzyme replacement therapy (ERT), an intravenous administration of recombinant enzymes, was initially developed as a treatment for Gaucher disease, and is now an established treatment modality for many LSDs, including MPS IV A (Lachmann 2011). In 2014, a recombinant human GALNS enzyme (rhGALNS, elosulfase alfa, BMN 110, Vimizim®, BioMarin Pharmaceutical Inc., USA) was approved by the US Food and Drug Administration for use. The use of ERT in MPS IV is generally considered safe, with few hypersensitivity reactions, and rare cases of anaphylaxis (Hendriksz 2014). Known adverse events are vomiting, pyrexia and headaches (Hendriksz 2016; Jones 2015).

How the intervention might work

In MPS IV A, similar to other LSDs such as Gaucher disease, a deficient or malfunctioning enzyme leads to the accumulation of its substrate, KS. ERT is the process of systemic administration of a synthetically-produced enzyme. The systemically administered enzyme enters the lysosomal compartment of different cells via mannose-6-phosphate receptors on the plasma membrane (Mistry 1996), a specific protein uptake mechanism.

Why it is important to do this review

As in other ultra-rare orphan disorders, the body of evidence for treatment efficacy in MPS IV is sparse. This can be explained by the low number of people with the disorder and their heterogeneity; the course of the disease (a chronic disorder with diverse manifestations); and the differences between study protocols. All of these inherent issues limit the ability to perform randomised controlled trials (RCTs). Rare disease populations are also spread over wide geographical areas of the world and this increases the number of clinical trial sites with small numbers of participants as an additional confounder. It is worthwhile mentioning that most of the evidence regarding treatment efficacy in fact comes from non-randomised studies (NRSIs), e.g. patient registries. For example, a PubMed search of MPS IV A and 'randomised controlled trial' as MeSH terms yields six results, while when combined with 'cohort studies' it results in 40 studies. Hitherto, the production of a valuable evidence-based systematic review on treatment efficacy using 'classical' Cochrane methodology is likely to be beset with many limitations, as discussed by the authors undertaking this review in a further Cochrane Review on Gaucher disease (Shemesh 2015). Here, we plan to perform a Cochrane Review incorporating data from both RCTs and NRSIs, to assess treatment efficacy for MPS IV A, and to conclude whether such an approach will benefit a systematic review of an ultra-rare disorder.

OBJECTIVES

1. To assess the effectiveness, safety and appropriate dose regimen of ERT in people with MPS IV A.

2. To determine whether evidence from NRSIs (which potentially offers longer follow-ups) can contribute to the ERT efficacy evidence-base, and to determine the potential need for additional RCT evidence.

3. To consolidate recommendations for the design of future clinical trials.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs (including open-label trials, cross-over trials and cluster randomised trials).

Since long-term effects are less likely to be evaluated in RCTs, because of the limited body of evidence emerging from RCTs on efficacy and safety in rare diseases, and in accordance to EPOC recommendations (EPOC 2017a), the following study designs will also be assessed (regardless of length of follow-up):

1. NRSIs;
2. prospective cohort studies;
3. controlled before-after studies.

Due to the lack of formal guidelines regarding the inclusion of NRSIs in Cochrane Reviews, two authors (ES, LD) will individually assess these studies and determine their eligibility for inclusion. Any uncertainties regarding eligibility for inclusion will be discussed by all authors.

Despite the beneficial potential these studies may hold for a systematic review, NRSIs are more likely to have intrinsic confounding factors, and thus are prone to bias. We will therefore assess included NRSIs for the presence of confounders:

1. age;
2. height;
3. walking ability (stratified to less than 30 m; 30 to 200 m; further than 200 m); and
4. previous surgical procedures.

Following the guidance provided in chapter 13 of the *Cochrane Handbook for Systematic reviews of interventions*, we will also consider whether participant selection was restricted or balanced in relation to these confounders and whether matching or adjustments were conducted in statistical analyses (Reeves 2011).

Types of participants

Individuals with MPS IV A of any age and of any disease severity.

Types of interventions

ERT with elosulfase alfa compared to placebo, or a comparison of different doses (e.g. 1 to 4 mg/kg).

Types of outcome measures

Primary outcomes

1. Endurance (measures of walking distance)
   i) six-minute walk test (6MWT)
   ii) three-minute stair climb test (3MSCT)
2. Safety and tolerability (reported side effects, development of antibodies to the enzyme)
3. Pulmonary function measures (absolute values)
   i) forced vital capacity (FVC) (litres)
   ii) maximum voluntary ventilation (MVV) (L/min)
   iii) forced expiratory volume in 1 second (FEV_1) (L)

Secondary outcomes

1. Weight (kg)
2. Urinary KS levels (μ mg/mg normalized for creatinine)
3. Quality of life (QoL) scores (measured by, e.g. the Health Assessment Questionnaire, and the EurQol 5D scales)
4. Pain (e.g. using the visual analogue scale (VAS))

We will prefer to analyse the continuous outcomes (endurance, pulmonary functions, weight, urinary KS levels, QoL scores and pain) as change from baseline. If data will not be sufficient, we will use post-treatment scores.

All outcomes, irrespective of original study design, will be assessed following the division to four time points. This division follows the length of the published studies:

1. up to six months;
2. six months and up to 12 months;
3. 12 months and up to 24 months;
4. 24 months and above.

Search methods for identification of studies

We will search for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

We will identify relevant studies from the Cystic Fibrosis and Genetic Group's Inborn Errors of Metabolism Trials Register using the term: mucopolysaccharidosis.

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.

In addition to the above, we will conduct a search of the following databases and trial registers:·

- PubMed (www.ncbi.nlm.nih.gov/sites/entrez; 1946 to present);·
- ClinicalTrials.gov (www.ClinicalTrials.gov);·
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/).

See Appendix 2 for the full search strategies.

Searching other resources

Reference lists

The reference lists of all included articles and relevant systematic reviews will be reviewed to identify any additional studies.

Handsearching and experts

We will search through abstract books of the Lysosomal Disease Network (LDN) conference (last five years), and contact experts in the field in attempt to retrieve any further relevant data.

Data collection and analysis

Selection of studies

Regardless of study design, two authors (ES, LD) will independently assess and discuss the papers identified by the initial searches in order to decide whether they meet the inclusion criteria. Should any disagreements on study eligibility arise, we will reach a consensus by consultation with the remaining three authors (CJH, CH, AK).

Data extraction and management

Two authors (ES, LD) will independently extract the data (with input from a third author as necessary (AK)) using standard data extraction forms which will include information about the following:

1. methods of the study (type of study, number of participants and dropouts);
2. characteristics of the study population;
3. type of intervention;
4. data for assessing the risk of bias:
   i) for RCTs: methods of randomisation, whether blinding was applied (and who was blinded), type of sequence generation used, and type of allocation concealment used);
   ii) for NRSIs: presence of potential confounders influencing assignment to interventions (1. age; 2. height; 3. walking ability (stratified to less than 30 m, 30 m to 200 m, further than 200 m); and 4. previous surgical procedures), loss to follow-up details, whether the selection of participants was biased, whether a deviation from intended interventions had occurred (performance bias);
5. outcomes and results (means, standard deviations (SDs) or standard errors (SEs)). In the case of non-randomised cohort studies, we will prefer to extract treatment effects for differences adjusted for baseline differences between groups in potential confounding factors.

If additional data are needed, we will contact study investigators or calculate the missing values (based on available data) or impute these (if possible).

Given that combining randomised and non-randomised evidence is not recommended due to fundamental differences in study design, we plan to analyse these different types of studies separately.

Assessment of risk of bias in included studies

We will assess the risks of bias using ROB 2.0 for RCTs, and using ROBINS-I for NRSIs.

RCTs

We will assess the included RCTs using the Cochrane risk of bias assessment tool, focusing on the following domains (Higgins 2011a).

Assessment of sequence generation

1. Low: if allocation sequence is suitable to prevent selection bias (i.e. computer-generated lists, coin tossing, shuffling cards or envelopes, random number table, etc.).
2. High: if allocation sequence could be related to prognosis and thus introduce selection bias (i.e. date of admission, clinical judgement, participant preference, results of laboratory tests, availability of intervention, date of birth, etc.).
3. Unclear: if there is insufficient information regarding the sequence generation.

Assessment of allocation concealment

1. Low: if investigators were shielded from predicting the assignment of participants into the intervention groups (i.e. central randomisation was done by telephone or by a pharmacy, identical and sequentially numbered drug containers or sequentially numbered, sealed and opaque envelopes).
2. High: if investigators were not shielded from predicting the assignment of participants into the intervention groups (i.e. non-opaque envelopes, open allocation schedule, etc.).
3. Unclear: if the method of concealment is not described.

Assessment of blinding

1. Low: if no blinding was done, but outcome was not likely to be influenced by the lack of blinding; or if blinding was ensured and was unlikely to be broken.
2. High: if no blinding was done, and outcome was likely to be affected by the lack of blinding; or blinding was attempted but could have been broken.
3. Unclear: if the method of blinding is not described.

Incomplete data

We will consider whether it was stated how many participants were lost to follow-up, and reasons for this given; also if loss to follow-up did occur, whether or not an intention-to-treat (ITT) analysis was performed. According to these criteria, we will define three levels of risk of bias as follows.

1. Low risk: if the number or reasons (or both) for loss to follow-up were mentioned, and if an ITT analysis was carried out.
2. High risk: if number or reasons (or both) for loss to follow up were not mentioned, or ITT analysis was not carried (or both).
3. Unclear risk: if the original study did not specify the way loss to follow-up was handled.

Selective outcome reporting

We aim to assess the consistency of outcomes which the original investigators planned to report during the study, to those actually reported within the published paper, by comparing the study protocols and registries with the information in the final publication. If the protocols are not available, we will compare the methods section of the publication to the published results, in order to assess whether all outcomes were indeed reported and to determine if selective outcome reporting occurred.

Other sources of bias

We will review relevant studies for other potential sources of bias, such as: deviation from study protocol; early cessation of the study; selective reporting of subgroups; or a bias due to poor delivery of the interventions.

NRSIs

We will assess the risk of bias in NRSIs using the ROBINS-I domains as below (Sterne 2016). The effect of assignment to intervention will be estimated. We will define five levels of risk for each domain.

1. Low risk of bias: the study is comparable to a well performed RCT, with regard to the specific domain being assessed.
2. Moderate risk of bias: the study has a solid methodology for a NRSI with regard to the specific domain being assessed, but cannot be considered comparable to a well-performed RCT.
3. Serious risk of bias: the study has important methodological problems with regard to the specific domain being assessed.
4. Critical risk of bias: the study has a severe methodological issue in the specific domain, which precludes the drawing of any useful evidence on the effects of intervention.
5. No information available to base a judgement about risk of bias for a specific domain.

Bias due to confounding

We will review whether one or more prognostic variables (as defined above in Data collection and analysis) also predicts the intervention received at baseline.

Bias in selection of participants

When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical This form of selection bias is distinct from confounding - a specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention.

Bias in classification of interventions

We will assess bias introduced by either differential or non-differential misclassification of intervention status.

Bias due to deviations from intended interventions

We will consider systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s).

Bias due to missing data

We will review whether later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors).

Bias in measurement of outcomes

We will review bias introduced by either differential or non-differential errors in measurement of outcome data.

Bias in selection of the reported results

Selective reporting of results, depending on the findings.
We will estimate an overall risk of bias utilizing the assessment of each of these domains. The overall risk of bias for NRSIs will follow the same division to five levels of bias.

1. Low risk of bias: the study is comparable to a well-performed RCT.
2. Moderate risk of bias: the study provides sound evidence for a NRSI, but cannot be considered comparable to a well-performed RCT.
3. Serious risk of bias: the study has some methodological issues.
4. Critical risk of bias: the study suffers from too many methodological issues, thus not providing any useful evidence and should not be included in the synthesis.
5. No information on which to base a judgement about risk of bias.

Measures of treatment effect

We will analyse adverse events as dichotomous data by calculating the odds ratio (OR) and 95% confidence intervals (CIs). For all other outcomes, given that we consider it likely that the original study reports will have utilised various scales and measurements to assess the relevant continuous outcomes, we plan to analyse the data by calculating the standardized mean difference (SMD) and the corresponding 95% CIs. If the studies do not report post-intervention results adjusted for baseline, but instead present absolute post-treatment data without baseline values (so it is not possible to calculate change data), we will consider using absolute post-treatment data instead.

We will synthesise and present all components within one outcome domain together.

Unit of analysis issues

For RCTs, when combining results from cross-over trials in a meta-analysis, we plan to use the methods recommended by Elbourne (Elbourne 2002). For studies with multiple treatment groups we will include subgroups that are considered relevant to the analysis. When appropriate, we will combine groups to create a single pair-wise comparison. If this is not possible, we will select the most appropriate pair of interventions and exclude the others (Higgins 2011b). For NRSIs, studies may measure data over multiple time points; given these data will have a correlated structure, we plan to analyse the data based on the pre-defined time periods (as with RCT data), adjusted for confounders (see Data extraction and management).

Dealing with missing data

If some of the numerical data are missing from the identified studies (e.g. SDs), we will contact the original investigators and request these data. If we are unable to retrieve these data, we will attempt to calculate missing data by utilising the available data (e.g. when a SD is not reported, it may be calculated based on given CIs, the mean, and the number of participants). If this is not possible, we will attempt to impute SDs based on similar studies (i.e. interventions, time points, population) (Higgins 2011b). For NRSIs, if information regarding confounders is missing, we will contact the original investigators for clarification. If we are unable to retrieve such information or estimate it based on similar cohorts, we will adapt the risk of bias for such studies accordingly.

Assessment of heterogeneity

In order to assess heterogeneity between studies, we will assess the forest plots visually, and will use the I^2 statistic (Higgins 2003) and the Chi^2 test and its corresponding P value, as stated in chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We will consider values of 0% to 50% as not important, 50% to 75% as moderate, and 75% to 100% as considerable heterogeneity.

Assessment of reporting biases

Where sufficient data are available (10 or more studies per outcome assessed), we will assess potential publication bias by constructing and assessing the symmetry of a funnel plot. If we detect asymmetry, we will explore causes other than publication bias.

Data synthesis

Given that combining randomised and non-randomised evidence is not recommended due to the fundamental differences in study design, we plan to analyse these different types of studies separately.

RCTs

For RCTs, we plan to use a fixed-effect model to synthesize the data (inverse-variance method). If the included trials are not sufficiently homogeneous to be combined in a meta-analysis, we will display the results of included studies in a forest plot, suppressing the pooled estimate.

NRSIs

Because of the likelihood presence of heterogeneity between NRSI we plan to use a random-effects model to synthesize the data, due to anticipated heterogeneity between cohort studies (emerging from different adjustment for confounders, covariates in adjusted models etc.).

If the included studies are not sufficiently homogeneous to be combined in a meta-analysis ($I^2 > 60\%$), we will display the results of included studies in a forest plot, suppressing the pooled estimate.

Subgroup analysis and investigation of heterogeneity

We aim to undertake a subgroup analysis by age (under and over 14 years of age). We intend to sub-divide our analysis using the age of 14 years as a cut-off since final growth of people with MPS IV is achieved by that age. Therefore, it would be of interest to analyse data from the period in which ERT is likely to have an effect on growth.

Sensitivity analysis

For both sets of analyses (RCTs and NRSIs), if there are at least 10 comparable studies, we will perform a sensitivity analysis by excluding those trials with an overall high risk of bias.

Summary of findings tables

The summary of findings tables will provide information regarding participant population, the interventions compared, the main results and the quality of these findings (based on risk of bias, inconsistency, indirectness, imprecision and publication bias). We will report the following main outcome measures.

1. Endurance
2. Pulmonary function measures
3. Anthropometric measures
4. Safety and tolerability
5. QoL score

Data from NRSIs will be presented separately; the quality of these studies will be considered 'low' to begin with, and may be upgraded if the following criteria are met:

1. dose response;
2. large size of the effect;
3. confounding reduces or increases the demonstrated effect.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Glossary of terms

Term	Definition
Macromolecule	A molecule composed of a very large number of atoms, such as proteins
Glycosaminoglycans	Macromolecules made up from protein and sugar molecules.
Catabolic process	A metabolic process that breaks down molecules into small units, which are then usable in the body systems
Pyrexia	A raise in body's temperature, also called fever by many people
Dysplasia	Abnormalities of usually the bones which may cause very abnormal looking features depending on which bones are affected

(*Continued*)

Pectus carinatum	A developmental anomaly characterized by abnormal anterior protrusion of the sternum (a bone in the chest) and adjacent costal cartilage; Also called pigeon chest
Kyphosis	Deformities of the spine characterized by an exaggerated convexity of the vertebral column which cause the spine to look more curved than normal
Odontoid hypoplasia	Improper development, or a complete absence, of a bony projection from the second cervical spinal bone. This process is like a peg; It helps to hold the top two parts of the spine together and protect the spinal cord from being squashed or damaged by allowing too much movement

Appendix 2. Search strategies

Database/ Resource	Strategy
PubMed (1946-present)	(Mucopolysaccharidosis iv[tw] OR Mucopolysaccharidosis iva[tw] OR Mucopolysaccharidosis ivb[tw] OR mps iv*[tw] OR *Morquio*[tw] OR "Mucopolysaccharidosis IV"[Mesh]) AND (enzyme replacement therapy[MeSH] OR (enzyme* AND replace*) OR elosulfase[tw] OR vimizim[tw])
ClinicalTrials.gov	CONDITION/ DISEASE: Mucopolysaccharidosis iv OR MPS iv OR Morquio OTHER TERMS: enzyme OR elosulfase OR vimizim
WHO International Clinical Trials Registry Platform (ICTRP)	Mucopolysaccharidosis iv* OR MPS iv* OR Morquio

CONTRIBUTIONS OF AUTHORS

ES, CH and CJH formulated the research questions. Outcomes and subgroup analyses were discussed by all authors. Writing of the first protocol draft was done by ES. The final version of the protocol was written by all authors. Data collection, analyses and bias assessments will be done by ES and LD, assisted by AK as required. Data interpretation will be done by all authors: CH and CJH will provide clinical perspectives, LD and ES will provide methodological insight and AK will provide statistical input. ES is regarded as the 'guarantor' of this review.

DECLARATIONS OF INTEREST

ES reports no possible conflict of interest.

LD reports no possible conflict of interest.

CJH Is consultant for all rare disease companies, patient organisations and regulators. Director of FYMCA Medical Ltd.

CH declares that she has received travel and accomodation support from Genzyme and Shire. She acts as advisor to the Dutch Medicines Evaluation Board and the National Health Care Institute. She is involved in the development of a protocol for conditional access for elosulfase alfa in the Netherlands. AMC has received support for Registries (Genzyme and Shire) and unrestricted educational as well as research grants.

AK reports no possible conflict of interest.

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