Idebenone for the treatment of Duchenne muscular dystrophy (Protocol)


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Idebenone for the treatment of Duchenne muscular dystrophy

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the efficacy of idebenone on muscle strength, muscle function, respiratory function, cardiac function and quality of life in people with Duchenne muscular dystrophy.
BACKGROUND

Description of the condition

Duchenne muscular dystrophy (DMD) is a life-limiting, X-linked neuromuscular disease with a prevalence rate of approximately 1 in 3,500 live male births. DMD is characterized by progressive skeletal muscle weakness and wasting, resulting in the loss of ambulation between ages of 7 and 13 years and death in the second or third decade from cardiac or respiratory failure (Klitzer 2005). Dystrophin, a 427 kDa cytoskeletal protein, is normally found at the inner surface of skeletal and cardiac muscle fibers. In humans, DMD is caused by defects in the dystrophin gene that prevent the production of dystrophin, leading to costamere disorganization, sarcolemmal fragility, muscle weakness and necrosis (Ervasti 2007). At present, there are still no effective interventions to alter significantly the progression of the disease. However, quality of life and life expectancy can be markedly improved if cardiopulmonary manifestations are adequately treated (Finsterer 2006). We should be optimistic that novel therapeutic agents may have a positive impact on this disease in the near future.

Description of the intervention

Idebenone is an organic compound of the quinone family, promoted commercially as a synthetic analogue of coenzyme Q10 (CoQ10). Idebenone has been used for research in neurological disorders. Several studies have indicated that idebenone might exert some therapeutic effects in Alzheimer’s disease (Weyer 1997; Gutzmann 1998; Gutzmann 2002). However, one study (Thal 2003) suggested that idebenone failed to slow cognitive decline in Alzheimer’s disease. At present, no systematic review has been performed on this topic and no convincing conclusions can be drawn. In participants with Friedreich’s ataxia, a phase III study demonstrated that treatment with higher doses of idebenone was generally well tolerated and associated with improvement in neurological function and activities of daily living (ADL) (Di Prospero 2007). In addition, idebenone is currently being investigated in Leber’s hereditary optic neuropathy, MELAS syndrome (Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes) and primary progressive multiple sclerosis.

On 20 March 2007, the European Commission granted orphan designation (EU/3/07/437) to Sanhera Pharmaceuticals (Germany) GmbH for idebenone in the treatment of DMD (Committee for orphan medicinal products 2007). Results of a long-term, blinded and placebo-controlled study in the dystrophin deficient mdx mouse demonstrated that long-term idebenone treatment initiated before the appearance of symptoms significantly prevented cardiac diastolic dysfunction, blocked the development of lethal acute heart failure during a dobutamine-mediated stress protocol (i.e. improved contractile reserve), reduced cardiac inflammation and fibrosis, and improved ventricular running performance (Buyse 2009). Authors of this trial concluded that they had identified a novel potential therapeutic strategy for homologous human DMD. The 12-month Phase II Efficacy and Tolerability of Idebenone in Boys With Cardiac Dysfunction Associated With Duchenne Muscular Dystrophy (DELPHI) trial has evaluated the efficacy and tolerability of idebenone at a dose of 450 mg/day compared to placebo in children with DMD (NCT00654784). Clinical efficacy of idebenone was demonstrated by improvement in functional cardiac and respiratory parameters (including the primary endpoint) that were sensitive markers of cardiac disease and respiratory insufficiency (Buyse 2008). The post hoc subgroup analysis of the DELPHI trial, which was intended to verify any potential influence of glucocorticoids on early markers of respiratory weakness in people with DMD, indicated that the effect size of idebenone on peak expiratory flow (PEF) was significantly larger in glucocorticoid-naïve participants than in glucocorticoid users (Buyse 2009a). A phase III randomized, double-blind, placebo-controlled clinical study of idebenone is planned (Duchenne Muscular Dystrophy Long-term Idebenone Study, DELOS), which aims to determine efficacy using a clinically meaningful early parameter of respiratory function in participants with DMD who are in their second decade (Buyse 2009b).

How the intervention might work

The beneficial effects of idebenone can be explained by its ability to protect against mitochondrial respiratory chain dysfunction and reduce oxidative stress (Buyse 2009; Gumperli 2009). Dystrophin and the dystrophin-associated proteins may be involved in cell survival signaling pathways that regulate antioxidant defense mechanisms (Disatnik 2000). Free radical production may be disrupted and contribute to the ensuing pathology (Tidball 2007). Excessive reactive oxygen species (ROS) production and simultaneous activation of abnormal Ca²⁺ signals amplify each other, finally culminating in a vicious cycle of damaging events, which may contribute to the abnormal stress sensitivity in dystrophic skeletal muscle (Shkryl 2009). With progression of weakness and wasting of striated skeletal muscles, inspiratory and expiratory muscles will eventually be impaired. Meanwhile, mitochondrial dysfunction and oxidative damage may be involved in the pathogenesis of heart failure (Williams 2007; Jung 2008). Furthermore, respiratory insufficiency may be worsened by left or right ventricular heart failure. Idebenone exerts its antioxidant function via various mechanisms. It can inhibit the oxidation of nicotinamide adenine dinucleotide (NADH)-dependent substrates (Rauchová 2008), decrease the generation of ROS (Rauchová 2006; Ranganathan 2009), reduce oxidative damage and mitochondrial swelling, and strongly increase glyceraldehyde dehydrogenase (G3PDH) activity (Haefeli 2009).
**Why it is important to do this review**

DMD is a devastating and still incurable neuromuscular disease. Increased oxidative stress within the cell that damages the sarcolemma is an important pathological characteristic of this dystrophin deficient disease. Several studies have proposed that idebenone may reduce oxidative stress and protect mitochondrial function. Meanwhile, preliminary data suggest beneficial effects on cardiac and respiratory function. Hence, idebenone seems to be a novel potential therapeutic strategy for DMD. The purpose of this review is to provide up-to-date evidence regarding the efficacy and adverse effects of idebenone in people with DMD.

**OBJECTIVES**

To evaluate the efficacy of idebenone on muscle strength, muscle function, respiratory function, cardiac function and quality of life in people with Duchenne muscular dystrophy.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

All relevant RCTs and quasi-RCTs will be eligible for inclusion. Quasi-RCTs are those using not truly random methods in the sequence generation process such as date of birth, date of admission, hospital or clinic record number. We will also include two-period cross-over trials.

**Types of participants**

We will include both ambulant and non-ambulant people with a definite diagnosis of DMD.

**Types of interventions**

We will consider trials comparing idebenone with placebo, other drug treatment and no treatment (e.g. standard care).

**Types of outcome measures**

**Primary outcomes**

Primary outcomes will be measured after 12 months and will be change in timed functional testing from baseline, such as time taken to walk 30 feet and time to climb four stairs, and change in muscle function from baseline as measured by functional rating scales like Hammersmith motor ability scale (HMAS) (Scott 1982), Brooke upper extremity scales (Brooke 1981), Vignos lower extremity scales (Vignos 1960) and Motor Function Measure (MFM) (Bérard 2005).

**Secondary outcomes**

1. Change in muscle strength from baseline after six months of treatment measured by manual muscle testing (MMT) such as Medical Research Council (MRC) strength scores (MRC 1976), and quantitative muscle testing (QMT) using equipment such as an isokinetic dynamometer or hand-held dynamometer.
2. Change in respiratory function from baseline as evaluated by percentage of expected forced vital capacity (FVC) for height and forced expiratory volume in one second (FEV1) after six months of treatment.
3. Change in cardiac function from baseline, such as fractional shortening (FS) or ejection fraction (EF) measured by echocardiography or gated magnetic resonance imaging or tissue doppler after six months of treatment.
4. Change in quality of life from baseline as measured by validated and recognized rating scales such as Short-Form 36 (SF36) (Ware 1993) and Barthel Index (BI) (Mahoney 1965) after six months of treatment.
5. Adverse events which lead to withdraw of treatment and serious adverse events which lead to hospitalization or death during the treatment and follow-up period.

**Participants with DMD have gradual loss of muscle function and concurrently develop progressive contractures over time. Six months to 12 months and greater than 12 months are appropriate times given the fact that studies of DMD therapeutics will be extremely long.**

**Search methods for identification of studies**

**Electronic searches**

We will search the Neuromuscular Disease Group Specialized Register using the following terms: muscular dystrophy, duchenn*, dystrophin*; idebenone, SNT-MC17, Catena. The strategy will be adapted to search MEDLINE (1966 to present), EMBASE (1980 to present), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and databases of ongoing trials including Current Controlled Trials, the National Research Register (NRR) archive and the US National Institutes of Health.

**Searching other resources**
We will search the bibliographies of any included studies that are identified for further references and will contact authors of identified trials for additional information and unpublished data.

**Data collection and analysis**

**Selection of studies**

Two review authors (Geng JS and Jiang K) will independently screen all the titles and abstracts of publications identified by the searches to assess their eligibility. They will exclude publications that do not meet the criteria at this stage. Following screening, they will assess the full text of eligible citations for inclusion. They will select trials and reach a final list of studies by consensus. The two authors will discuss and resolve any disagreements where possible. If there is no consensus, they will consult a third member of the team (Wu TX).

**Data extraction and management**

Two reviewers (Geng JS and Jiang K) will independently extract characteristics of each included trial including the risk of bias assessment, baseline characteristics and results for the outcome measures using the standard data extraction form developed by the Cochrane Neuromuscular Disease Group. When additional data are required, we may contact the authors for relevant information.

For continuous data, the summary statistics required for each trial and each outcome are the mean change from baseline, the standard deviation (SD) of the mean change, and the number of participants for each group. When studies do not report changes from baseline, we will extract the mean, SD and the number of people for each group at each time point. If any of the continuous data which did not report the SD and this could not be deduced, then the standard error (SE) will be deduced and estimates from the individual studies.

For dichotomous data, we will seek the numbers in each group at baseline and post-treatment and other measurement time points. For an intention-to-treat analysis, we will collect data for each outcome measure on every participant randomized, irrespective of compliance.

For cross-over studies, we will extract the mean change from baseline and the SD or SE for each group. We will seek information about randomized participants excluded from the published analyses and if available incorporate it into the analysis.

**Assessment of risk of bias in included studies**

Two review authors (Geng JS and Shi LL) will assess the risk of bias of each trial according to the approaches described in The Cochrane Handbook for Systematic Reviews of Interventions 5.0.1 (Higgins 2008). We will construct ‘Risk of bias’ tables using the Cochrane Collaboration software, Review Manager 5 (RevMan 2008). The risk of bias will be assessed as: yes (low risk of bias); no (high risk of bias); or unclear (uncertain risk of bias). The following characteristics will be evaluated:

1. Adequate sequence generation?
2. Allocation concealment?
3. Blinding?
4. Incomplete outcome data addressed?
5. Free of selective reporting?
6. Free of other bias?

The assessment of the quality of the body of evidence will follow the methods recommended by Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (Atkins 2004; Higgins 2008), which combines considerations of risk of bias, directness, heterogeneity, precision and publication bias. Using Gradeprofiler (version 3.2.2) (GRADEpro 2008), we will construct a Summary of findings’ table, which includes information on the individual selected outcomes, the amount of evidence available to make the judgement, the relative and absolute risks and the quality of the evidence used for each outcome to make the judgement. Outcomes to be included in the 'Summary of findings’ table will be: change in muscle function, change in muscle strength and incidence and severity of adverse effects.

**Measures of treatment effect**

Statistical methods used to measure treatment effect will be in accordance with The Cochrane Handbook for Systematic Reviews of Interventions 5.0.1 (Higgins 2008).

For continuous data, the main outcomes of interest is the change in score from baseline to the final assessment. If the change from baseline results is not reported, we will calculate the statistics from baseline, if data are available. We will use the mean difference (MD) with 95% confidence intervals (CIs) where outcomes are measured in a standard way across studies. We will use standardized mean differences (SMD) with 95% CIs to summarise results across studies with outcomes that are conceptually the same but measured in different ways.

For dichotomous data, we will use the risk ratio (RR) with 95% CIs.

For cross-over studies, we will calculate the paired MD or the paired SMD between treatments and their SE.

**Unit of analysis issues**

For trials comparing more than two intervention groups, we will assess the relevant intervention group. Cross-over studies in which each participant acts as his or her own control and in which every participant receives every intervention have advantages over parallel group trials. The effect estimate for the meta-analysis will be the mean and SE of the differences between experimental and control groups. The effect estimate may...
be included in a meta-analysis using the generic inverse variance (GIV) method in RevMan.

In cluster-randomized studies, groups of individuals are randomized to different interventions. The multi-level statistical models should be used in the analysis of cluster-randomized trials. Effect estimates and their SEs from correct analyses of cluster-randomized trials may be meta-analysed using the GIV method in RevMan.

**Dealing with missing data**

We will contact the chief investigators to request missing data. We will include in the review some studies that are lacking information on outcomes of interest, or summary data such as sample sizes, numbers of events, or SEs but we will not consider them in the meta-analysis. We will address the potential implications of missing data (e.g. loss to follow-up and no outcome obtained, receiving the wrong treatment, lack of compliance, or eligibility) in the "Discussion".

**Assessment of heterogeneity**

We will test heterogeneity of intervention effects among trials using the standard Chi² statistic (P value) or the I² statistic. P values of less than 0.10 will be taken as evidence of heterogeneity. We will interpret I² for heterogeneity as follows:

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

We will investigate heterogeneity among trials by excluding trials of the poorest quality in the analyses, and using the subgroup analysis as described below.

**Assessment of reporting biases**

We will draw a funnel plot to detect the possibility of publication bias in the meta-analysis if there are a reasonable number of studies (in accordance with methods developed by Cochrane Neuromuscular Disease Group: at least 10 is probably necessary for a clear pattern to emerge).

**Data synthesis**

If there is no substantial or considerable heterogeneity, we will synthesize the results in a meta-analysis. We will combine trial data using RevMan. We will used fixed-effect or random-effects models as appropriate.

For cross-over studies, only outcomes where results from the paired t-tests are available will be included for meta-analysis. We will calculate the paired mean difference and SE of change score from baseline to the final assessment. The GIV method will be used to combine data from cross-over studies with those from parallel group trials.

**Subgroup analysis and investigation of heterogeneity**

Subgroup analysis of interest will be ambulant versus non-ambulant DMD participants. Outcomes that depend upon ambulation will only include participants who can ambulate at the commencement of the trial. However, we will not perform subgroup analysis unless we can extract sufficient data about these two participant types.

**Sensitivity analysis**

We will detect the robustness of the results of the meta-analysis according to methods developed by Cochrane Neuromuscular Disease Group as follows.

1. Repeat the analysis excluding unpublished studies if there are any.
2. Repeat the analysis excluding studies of the lowest quality.
3. If there are any very large studies, repeat the analysis excluding them to look at how much they dominate the results.
4. Repeat the analysis excluding other types of studies, depending on the degree to which there are choices about the inclusion/exclusion criteria (for example with/without trials that had different age groups, different dosages, or different cut-offs for severity of disability).

**Acknowledgements**

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Additional references

Atkins 2004

Brooke 1981

Buyse 2008

Buyse 2009

Buyse 2009a

Buyse 2009b

Béard 2005

Committee for orphan medicinal products 2007

Di Prospero 2007

Disatnik 2000

Ervasti 2007

Finsterer 2006

Gemperli 2009

GRADEpro 2008

Gutzmann 1998

Gutzmann 2002

Haeffeli 2009

Higgins 2008
Jung 2008

Klitzner 2005

Mahoney 1965

MRC 1976

NCT00654784

Ranganathan 2009

Rauchová 2006

Rauchová 2008

RevMan 2008

Scott 1982

Shkryl 2009

Thal 2003

Tidball 2007

Vignos 1960

Ware 1993

Weyer 1997

Williams 2007

* Indicates the major publication for the study
APPENDICES

Appendix 1. MEDLINE (OvidSP) search strategy

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 drug therapy.fs.
6 randomly.ab.
7 trial.ab.
8 groups.ab.
9 or/1-8
10 exp animals/ not humans.sh.
11 9 not 10
12 exp muscular dystrophies/ or muscular dystrophy, duchenne/
13 duchenne.tw.
14 Dystrophin/
15 dystrophin$1.tw.
16 or/12-15
17 idebenone.mp.
18 exp Quinones/
19 ide.mp.
20 snt-mc17.mp.
21 catena.mp.
22 or/17-21
23 11 and 16 and 22

WHAT'S NEW

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HISTORY

Protocol first published: Issue 8, 2010

Idebenone for the treatment of Duchenne muscular dystrophy (Protocol)
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CONTRIBUTIONS OF AUTHORS

Geng JS - Drafting protocol and review versions; search for trials; selection of trials for inclusion/exclusion; assessment of risk of bias in included studies; extraction of data; interpretation of data analyses; updating review.

Dong JC - Data extraction and management; drafting review versions; updating review.

Jiang K - Drafting protocol versions; selection of trials for inclusion/exclusion; extraction of data.

Shen LH - Updating review.

Wu TX - Arbiter of selection of trials for inclusion/exclusion; methodology expert.

Ni HJ - Obtaining copies of trial reports.

Shi LL - Assessment of risk of bias in included studies.

Wang GH - Updating review.

Wu HQ - Updating review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Medical School of Nantong University, China.

External sources

- No sources of support supplied