Enzyme replacement therapy for Fabry disease: a systematic review of available evidence

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CRD summary
This study concluded that data available were more robust for enzyme replacement therapy in patients with Fabry disease at 1mg/kg compared with 0.2mg/kg every other week. Beneficial effects with either dose or preparation were variable. The possibility of missing studies, unclear study quality and the lack of reporting of the review process mean these conclusions should be viewed with caution.

Authors' objectives
To evaluate the efficacy of enzyme replacement therapy (specifically agalsidase beta compared with agalsidase alpha) in patients with Fabry disease.

Searching
MEDLINE and EMBASE were searched from inception to May 2009 for English-language studies. Search terms were reported.

Study selection
Prospective open-label or double-blind clinical studies that evaluated enzyme replacement therapy (agalsidase beta compared with agalsidase alpha) and reported quantifiable endpoints in patients with Fabry disease were eligible for inclusion.

The included studies were of agalsidase alpha (0.2mg/kg every other week in most studies, where reported) and agalsidase beta (doses varied, most were 0.1mg/kg every other week). Most studies focused on male patients. Some studies were conducted in children. Study duration ranged from 10 weeks to 54 months. Plasma GL-3 levels and accumulation in the kidney, heart and skin were most commonly study endpoints, followed by the renal endpoints of proteinuria and glomerular filtration rate.

The authors did not state how the papers were selected for the review.

Assessment of study quality
The authors did not state that they performed validity assessment.

Data extraction
The authors did not state how many reviewers performed data extraction.

Methods of synthesis
A narrative synthesis was presented and individual study details were reported in tables.

Results of the review
Thirty-two studies were included in the review: 23 open-label studies (n=682) and nine randomised placebo-controlled studies (n=311, range six to 82).

GL-3 accumulation:
Agalsidase beta and agalsidase alpha were associated with significant decreases in mean plasma GL-3 levels in three out of four RCTs and four out of nine open-label studies.

Normalisation of GL-3 in renal cells using agalsidase beta (1.0mg/kg every other week) was reported in one of two RCTs and four out of four open-label studies; no treatment effect of agalsidase alpha was found in one RCT.

Small, non-significant reductions in urinary GL-3 excretion were reported in three out of three open-label studies.
Cardiac GL-3 was significantly reduced with agalsidase beta in one RCT that reported this endpoint; agalsidase alpha did not significantly reduce cardiac GL-3 (one RCT).

Agalsidase beta was associated with positive effects on GL-3 clearance in the skin in two RCTs and three open-label studies.

The most common adverse events with enzyme replacement therapy were mild to moderate infusion reactions.

Further results (including results for important subgroups) were reported in the paper.

Authors' conclusions
The data available were more robust for enzyme replacement therapy at 1mg/kg compared with 0.2mg/kg every other week. The beneficial effects of enzyme replacement therapy with either dose or preparation were variable.

CRD commentary
The research question was supported by inclusion criteria for participants, study design and intervention. Criteria for outcomes were broad. Only English-language studies were sought and unpublished sources did not appear to be searched, so language and publication bias could not be ruled out. The review process was not described, so any steps taken to reduce reviewer error and bias were unknown. Study quality was not assessed, so the reliability of the primary studies was unknown. Narrative synthesis appeared appropriate given the diversity of outcomes reported.

The authors’ conclusions should be viewed with caution because relevant studies may have been missed, study quality was unclear and the review process was not reported fully.

Implications of the review for practice and research
Practice: The authors stated that patients with Fabry disease should be identified without undue delay and the patients' family should be screened for undiagnosed Fabry disease. Clinical results of enzyme replacement therapy needed long-term monitoring.

Research: The authors stated that further research was needed to address the role of enzyme replacement therapy at different stages. Outcomes should be reported in a consistent way. Specific gaps in knowledge were related to the clinical relevance of clearance of GL-3 accumulation, role of neutralising agalsidase antibody activity, when to start therapy and whether early intervention enhanced clinical benefits and prevented major organ damage.

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