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UFRGS PROPESQ
XXXI SIC
Salão UFRGS 2019 – Conhecimento o Formação o Inovação
21 . 25 . OUTUBRO . CAMPUS DO VALE

A Systematic Literature Review of Enzyme Replacement Therapy for Early and Late-Onset Pompe Disease

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Introduction

Pompe disease (PD) is an inherited lysosomal storage disorder characterized by deficiency of acid alpha-glucosidase that prevents the breakdown of glycogen into glucose, leading to the progressive accumulation of glycogen in and tissues of the body **(Table 1)**. Previous systematic review (SR) on early-onset PD (EOPD) and on late-onset PD (LOPD) haven't evaluated important endpoints for enzyme replacement therapy (ERT), thus creating the need for reassessing clinical outcomes.

Objectives

To evaluate efficacy and safety of alglucosidase alfa for EOPD and LOPD.

Methods

We systematically searched for studies published until September 2018, using the following search strategy:

- Pubmed: "Glycogen storage disease type ii" and "alpha-glucosidases"
- Embase: ('Glycogen storage disease type 2'exp) and ('recombinant glucan 1,4 alpha glucosidase'/exp or 'recombinant glucan 1,4 alpha glucosidase')

Outcomes of interest were defined a priori **(Table 2)**. Assessment of quality of evidence (QOE) was performed according to GRADE. This study is registered in Prospero under the numbers 123700 AND 135102.

Table 2: Outcomes defined a priori

EOPD: Cardiomyopathy, Time to Onset Ventilation, Myocardial Function, Safety, Survival, Neuropsychomotor Development, Quality of Life (QOL), Hypotonia, Swallowing Disorder.
LOPD: 6-minute-walking-test, Forced Vital Capacity, Safety, Muscle Strength, Quality of life, Walton Gardner Medwin Score, Ventilation hours/day, Survival, Sleep quality, Swallowing.

For the evaluation of the effectiveness of ERT in both forms of PD, the first inclusion criterion is being a randomized controlled trial (RCT). If fewer than five RCTs are identified, open-label and nonrandomized trials, controlled or uncontrolled (quasi-experimental), including ≥ five patients, and evaluating relevant outcomes defined a priori, will also be included.

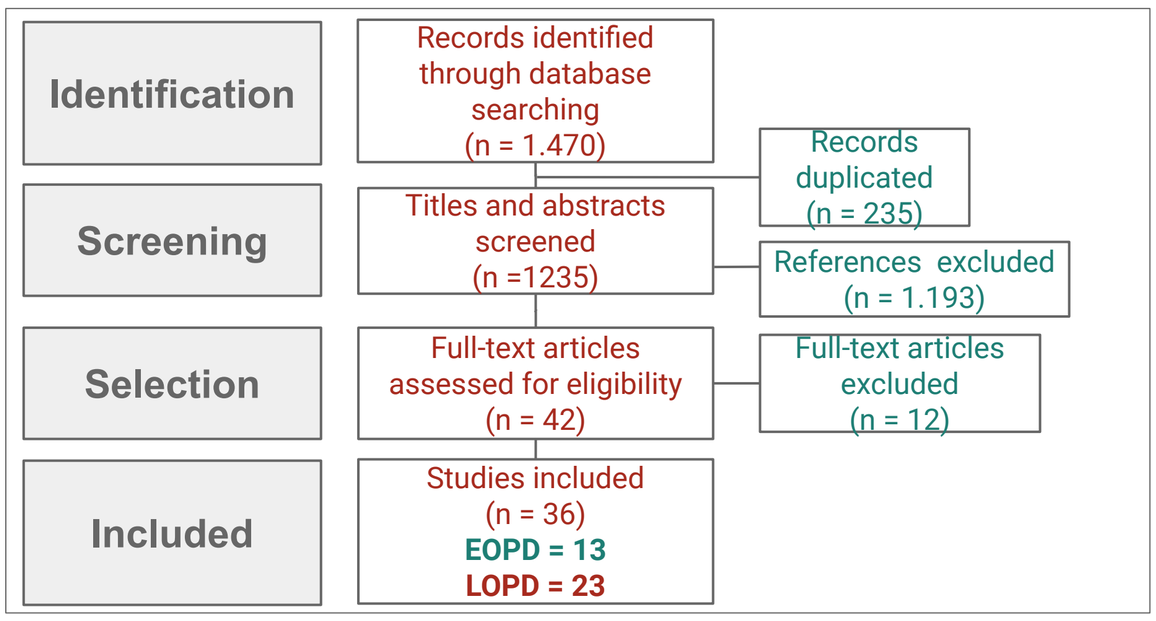

Figure 1: PRISMA flowchart of search results.

Table 1: Main clinical manifestations of Pompe disease

EOPD	• Onset before 12 months; • Cardiac Hypertrophy;	• Generalized muscle weakness.
LOPD	• Onset after 12 months; • Myopathy; • Respiratory distress (fadigue, sleep apneia)	• Proximal muscle weakness.

EOPD= early-onset Pompe disease; LOPD= late-onset Pompe disease

Results

The search results and the selection of articles are described in **Figure 1**. **EOPD** results are described in **Table 3** and **LOPD** results are described in **Table 4.**

Table 3 - EOPD Analyzed Endpoints

Survival	TOV*	Safety	Cardiomyopathy
Evaluated in 6 studies and increased in all of them (QOE very low).	Evaluated in 7 studies and 4/7 showed its increase by ERT (QOE very low)	6 studies described (QOE very low). All studies analyzed antibody formation, present in at least 85% of patients evaluated.	Evaluated in 10/13 by left ventricular mass, reduced in 10/13 studies after ERT (QOE very low).

TOV - Time to Onset Ventilation

Table 4 - LOPD Analyzed Endpoints

Quality of Life (QOL)	6MWT	Muscle strength (MS)	Safety
Evaluated in 6 studies and 5/6 used the SF-36 questionnaire, with very low QOE that favors ERT.	Patients under ERT showed improvement in all 12 studies (QOE very low).	Evaluated in 8 studies and 2/8 were unable to show improvement after ERT (very low QOE).	Described in 5 studies (QOE very low). In 4/5 studies all patients developed antibodies (QOE very low).

In both **EOPD** and **LOPD**, antibody titers were not correlated with severe adverse events (AEs) or infusion-associated reactions (IARs) nor were associated with treatment efficacy and clinical outcomes. Most IARs were mild to moderate in both cases.

Discussion/Conclusions

Despite very low QOE, our results add information over previous published studies on ERT:

- EOPD: ERT is beneficial for survival, cardiomyopathy and TOV;
- LOPD: the results corroborate previously published SR on ERT impact on 6MWT and show positive effect on QOL and MS;
- ERT is safe in both forms, once most AEs were mild to moderate and antibody formation did not seem to interfere with any outcome evaluated;
- Moreover, one should take into account that it is a rare disease.

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