ARTIGO DE REVISÃO
REVIEW ARTICLE

Critical appraisal of observational studies on enzyme replacement therapy for Gaucher's Disease

Avaliação crítica dos estudos observacionais da terapia de reposição enzimática para Doença de Gaucher

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Keywords:
Gaucher disease,
observational study,
enzyme replacement therapy

ABSTRACT

Objective: The objective of this study was to critically appraise the validity of observational studies on enzyme replacement therapy for Gaucher's disease. **Methods:** A literature search was performed in electronic databases without limits of date and for patients with confirmed Gaucher's Disease, regardless of age, receiving enzyme replacement therapy (alglucerase, imiglucerase, velaglucerase, or taliglucerase). Outcomes of interest were haemoglobin, platelet count, liver and spleen volume , plasma chitotriosidase, bone parameters, and antibodies production. The Newcastle-Ottawa tool was used for quality assessment, and the Oxford Centre for Evidence-based Medicine guidelines were used to assess the level of evidence. **Results:** Nineteen studies were selected. Studies with more comprehensive and recent data from the International Collaborative Gaucher Group (ICGG) Gaucher Registry were analyzed. Fifteen studies were from patients who used alglucerase or imiglucerase, including data of 757 patients after 10 years of use. Data on velagucerase treatment were restricted to four studies with 24 children and 8 adults after 2 and 7 years of follow-up, respectively. Only the French Gaucher's disease registry presented results for one patient using taliglucerase. The level of evidence was 2C for fourteen studies, 2B for one study, and 4 for four studies. **Conclusion:** Critical appraisal of observational studies revealed important and good quality data on imiglucerase treatment effectiveness and long-term safety. Although there are other treatment options (velaglucerase and taliglucerase), the lack of long-term observational data does not enable comparisons of the results in real world settings.

Palavras-chave:
Doença de Gaucher,
estudos observacionais,
terapia de reposição de enzimas

RESUMO

Objetivo: Realizar análise crítica sobre validade dos estudos observacionais de terapia de reposição enzimática para doença de Gaucher. **Métodos:** A busca na literatura foi realizada nas bases de dados eletrônicas sem limites de data e para pacientes com doença de Gaucher confirmada, de qualquer idade e recebendo terapia de reposição enzimática (alglucerase, imiglucerase, velaglucerase ou taliglucerase). Os desfechos de interesse foram hemoglobina, plaquetas, volume do fígado e do baço, quitotriosidase plasma, parâmetros ósseos e formação de anticorpos. A ferramenta Newcastle-Ottawa foi utilizada para avaliação da qualidade e os guias do The Oxford Centre for Evidence-based Medicine foram usados para classificar o nível de evidência. **Resultados:** Dezenove estudos foram selecionados. Foram analisados os dados mais completos e recentes do International Collaborative Gaucher Group Gaucher Registry. Quinze estudos incluíram pacientes que utilizaram alglucerase ou imiglucerase, incluindo dados de 757 pacientes com 10 anos de uso. Os dados sobre o tratamento com velagucerase foram restritos a quatro estudos com 24 crianças e 8 adultos após 2 e 7 anos de acompanhamento, respectivamente. Somente o French Gaucher's disease registry apresentou os resultados de um paciente com taliglucerase. O nível de evidência foi classificado como 2C em quatorze estudos, 2B para um estudo e 4 para quatro estudos. **Conclusão:** A avaliação crítica dos estudos observacionais com imiglucerase revelou dados importantes e de boa qualidade sobre efetividade e segurança do tratamento no longo prazo. Apesar de existirem outras opções de tratamento (velaglucerase e taliglucerase), a falta de dados observacionais a longo prazo não permite comparações dos resultados no mundo real.

Recebido em: 08/11/2015. **Aprovado para publicação em:** 19/11/2015
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Apoio financeiro: Este trabalho recebeu auxílio financeiro da Genzyme, e-mail: denizarvianna@gmail.com

Introduction

The ultimate goal of evaluations of healthcare interventions is to produce valid estimates of effectiveness, in terms of both internal and external validity. Internal validity is related to the extent to which the results of a study can be reliably attributed to the intervention under evaluation, whereas external validity is related to the extent to which the results of a study can be generalized beyond the given context of the study (Deeks, 2003).

Randomized controlled trials are considered the gold standard because minimization of bias is inherent to their design . However, in the scenario of rare diseases, because of the small number of individuals affected, it is often difficult to enroll enough patients in this kind of trial.

Alternate designs can address concerns about randomized controlled trials by using external or historical controls. In this case, all patients recruited in a proposed study receive the new or experimental therapy and their outcomes are compared with a population that had already been treated with the standard therapy. Observational studies, such as registries, are very useful to analyse clinical benefits of treatments in rare disease scenario.

Gaucher's disease, one of the most common lysosomal storage diseases, is an autosomal recessive condition caused by a deficiency of glucocerebrosidase, a lysosomal enzyme that hydrolyzes glucocerebroside, an intermediate in glycolipid metabolism. This deficiency results in the accumulation of glucocerebrosides within cells of the macrophage-monocyte system, particularly those of the spleen, liver, kidneys, lungs, brain, and bone marrow. Treatment for Gaucher's disease focuses on reducing stored glucocerebroside by replacing glucocerebrosidase with a recombinant active form of the enzyme via regular intravenous infusions.

Currently, the Brazilian Unified Health System reimburses treatment costs for three Enzyme Replacement Therapies (imiglucerase, taliglucerase alpha, velaglucerase alpha) for patients with Gaucher's disease.

The objective of this study was to critically appraise the validity of observational studies on enzyme replacement therapy for Gaucher's disease.

Methods (Review of the literature)

Database search strategy

The search was performed in the following electronic databases: Medline via Pubmed, LILACS, and the Cochrane Library, in September, 2015

Descriptors used in the review were selected using MeSH terms (Pubmed's Medical Subject Headings.). The search was performed in English, using the following descriptors: "Gaucher Disease" AND "Enzyme Replacement Therapy" ("Enzyme Replacement Therapies";"Replacement Therapies, Enzyme"; "Replacement Therapy, Enzyme"; "Therapies, Enzyme Replacement") OR "Imiglucerase"("Cerezyme"); "Alglucerase", "Taliglucerase alpha", "Velaglucerase alpha".

Population and Interventions

Studies were selected when they involved patients with confirmed Gaucher's Disease, regardless of age, receiving enzyme replacement therapy (alglucerase, imiglucerase, velaglucerase or taliglucerase). Substrate reduction therapy was not included.

Outcomes

Hemoglobin, platelet count, liver and spleen volume , plasma chitotriosidase, bone parameters, antibodies formation were the outcomes analyzed.

Inclusion and Exclusion criteria

Only Observational studies were analyzed. Randomized controlled trials, quasi-randomized studies, and cross-over studies were excluded.

Study selection

Abstracts were screened according to the eligibility criteria described in the Inclusion criteria section. Abstracts were independently screened by two reviewers, and any difference in inclusion and exclusion criteria were discussed. The same screening process was also applied to full paper review.

Quality Assessment

We used the Newcastle-Ottawa tool (Wells GS) to analyze observational studies for enzyme replacement therapy for Gaucher's disease. The Newcastle-Ottawa tool is designed for use in epidemiological systematic reviews, and can be used as either a scale or a checklist. The tool contains eight items, categorized into three groups: selection, comparability, and outcome (Table 1). A star system is used to enable a visual semi-quantitative assessment of study quality, in a way that the highest quality studies are awarded a maximum of one star for each item within the selection and outcome categories, and a maximum of two stars for comparability.

Level of Evidence

The Oxford Centre for Evidence-based Medicine (March 2009) was used to analyse the level of evidence.

Results

Nineteen studies were selected for analysis. The studies with more comprehensive and recent data from the International Collaborative Gaucher Group (ICGG) Gaucher Registry were analyzed. Some studies were excluded because they focused on other outcomes, such as reproductive events.

Table 1. Newcastle-Ottawa Quality Assessment Scale - cohort studies

Selection	
1	Representativeness of the exposed cohort a) truly representative of the average _____ (describe) in the community * b) somewhat representative of the average _____ in the community * c) selected group of users; e.g., nurses, volunteers d) no description of the derivation of the cohort
2	Selection of the non-exposed cohort a) drawn from the same community as the exposed cohort * b) drawn from a different source c) no description of the derivation of the non-exposed cohort
3	Ascertainment of exposure a) secure record (e.g., surgical records) * b) structured interview * c) written self-report d) no description
4	Demonstration that outcome of interest was not present at start of study a) yes * b) no
Comparability	
1	Comparability of cohorts on the basis of the design or analysis a) study controls for _____ (select the most important factor) * b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
Outcome	
1	Assessment of outcome a) independent blind assessment * b) record linkage * c) self-report d) no description
2	Was follow-up long enough for outcomes to occur? a) yes (select an adequate follow-up period for outcome of interest) * b) no
3	Adequacy of follow-up of cohorts a) complete follow-up - all subjects accounted for * b) subjects lost to follow-up unlikely to introduce bias - small number lost - > _____ % (select an adequate %) follow-up, or description provided of those lost) * c) follow-up rate < _____% (select an adequate %) and no description of those lost d) no statement

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The critical appraisal results using the Newcastle-Ottawa Quality Assessment Scale were separated by medication (alglucerase or imiglucerase, velaglucerase, and taliglucerase), and are shown in Tables 2, 3, 4, and 5. The classification by level of evidence is presented in Table 6.

Discussion

Recently, a systematic review was carried out to summarize all available randomized controlled study data on the efficacy and safety of enzyme replacement therapies and substrate reduction therapy for treating Gaucher's disease (Shemesh, 2015). The results reflect the limitations of analyzing evidence only in prospective randomized controlled trials, especially when dealing with chronic rare diseases (low number of studies and participants). The analysis emphasizes the need to determine whether it is realistic to carry out multi-decade prospective clinical trials for rare diseases, such as type 1 Gaucher's disease. With large treatment effects on the classical manifestations of the disorder, therapeutic investigations in Gaucher's disease should consider innovative trial designs and methodology to secure decisive data concerning long-term efficacy and safety.

Observational cohort studies or patient registry are being conducted over the last years, and although considered of lesser methological quality than randomized controlled trials,

Table 2. Critical appraisal of the validity of observational studies using alglucerase or imiglucerase (2002-2010)

Study	Weinreb 2002	Goldblatt 2005	Wenstrup 2007	Grigorescu Sido 2007	Andersson 2008	Sims 2008	Krug 2010
Selection							
1	a⁻	b⁻	a⁻	b⁻	a⁻	a⁻	c
2	NA	NA	a⁻	NA	NA	NA	NA
3	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻
4	b	b	a⁻	b	b	b	b
Comparability							
1	NA	NA	a⁻	NA	NA	NA	NA
Outcome							
1	b⁻	b⁻	b⁻	b⁻	b⁻	b⁻	b⁻
2	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻
3	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻	b⁻

NA: Not Available. Single cohort with no control arm

Table 3. Critical appraisal of the validity of observational studies using alglucerase or imiglucerase (2011-2014)

Study	Mistry 2011	Ciana 2012	Stirnemann* 2012	Weinreb 2013	Anderson† 2014	Camelo Jr 2014	Souza 2014	Sechi 2014
Selection								
1	a⁻	a⁻	a⁻	a⁻	b⁻	a⁻	c	c
2	NA	NA	NA	NA	NA	NA	NA	NA
3	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻
4	b	b	b	b	b	b	b	b
Comparability								
1	NA	NA	NA	NA	NA	NA	NA	NA
Outcome								
1	b⁻	b⁻	b⁻	b⁻	b⁻	b⁻	b⁻	b⁻
2	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻
3	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻	a⁻	b⁻

NA: Not available. Single cohort with no control arm
*The French Gaucher's disease registry: Among the 378 patients with follow-up, 298 (78.8%) received treatment. Alglucerase for 62 (20.8%) patients and imiglucerase for 224 (75.2%).
†Of the 22 patients on imiglucerase at recruitment, two patients switched to velaglucerase alpha during the ERT shortage crisis

they provide relevant information about the natural history of the disease, and effectiveness and safety of treatments.

In this analysis, due to longer market availability and use in many countries, the vast majority of records were from patients who used alglucerase or imiglucerase, including data of 10 years of follow-up with imiglucerase treatment in 757 patients (Weinreb, 2015). Data on velagucerase treatment showed just 8 adult patients (Zimram, 2015) that completed 7 years of use, and 24 children (Smith, 2015) that used the treatment for 2 years and had been previously treated with imiglucerase. The French Gaucher's disease registry (Stirnemann, 2012) presented results of one patient with taliglucerase, which was expected, given the shorter time in the market of this drug. The analysis of enzyme replacement therapy outcomes for Gaucher's disease is beyond the scope of this study.

Conclusion

Critical appraisal of observational studies revealed important and good quality data on imiglucerase treatment effectiveness and long-term safety. Although there are other treatment options (velaglucerase and taliglucerase), the lack of long-term observational data does not enable comparisons of the results with real world settings.

Table 4. Critical appraisal of the validity of observational studies using velaglucerase (2012-2015)

Study	Stirnemann*, 2012	Pastores, 2014	Smith, 2015	Zimran, 2015
Selection				
1	a⁻	a⁻	b⁻	b⁻
2	NA	NA	NA	NA
3	a⁻	a⁻	a⁻	a⁻
4	b	b	b	b
Comparability				
1	NA	NA	NA	NA
Outcome				
1	b⁻	b⁻	b⁻	b⁻
2	a⁻	a⁻	a⁻	a⁻
3	a⁻	b⁻	a⁻	b⁻

NA: Not Available. Single cohort with no control arm
*The French Gaucher's disease registry: Among the 378 patients with follow-up, 298 (78.8%) received treatment. Velaglucerase only for 4 patients (13.4%).

Table 5. Critical appraisal of the validity of observational studies using taliglucerase (2015)

Study	Stirnemann* 2012
Selection	
1	a⁻
2	NA
3	a⁻
4	b
Comparability	
1	NA
Outcome	
1	b⁻
2	a⁻
3	a⁻

NA: Not Available. Single cohort with no control arm
The French Gaucher's disease registry: Among the 378 patients with follow-up, 298 (78.8%) received treatment. Taliglucerase only for one patient (0.3%).

Table 6. Observational studies - Levels of evidence (Oxford Center for Evidence-Based Medicine)

Studies	Levels of evidence	
Weinreb 2002; Goldblatt 2005; Andersson 2008; Sims 2008; Mistry 2011; Stirnemann 2012; Weinreb 2013; Anderson 2014; Camelo Jr 2014; Souza 2014; Sechi 2014; Pastores 2014; Smith 2015; Zimran 2015	2C	Outcomes research
Wenstrup 2007	2B	Single cohort study, Retrospective cohort study or poor follow-up
Grigorescu Sido 2007; Krug 2010; Ciana 2012; Souza 2014	4	Case-series

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