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Effect of anti-laronidase antibodies on efficacy and safety of laronidase enzyme replacement therapy for MPS I: A comprehensive meta-analysis of pooled data from multiple studies

Yong Xue [a], Susan M. Richards [b], Asif Mahmood [c], Gerald F. Cox [d,*]

[a] Clinical Development, Rare Diseases Group, Sanofi Genzyme, Naarden, The Netherlands
[b] Clinical Laboratory Sciences, Sanofi Genzyme, Framingham, MA, USA
[c] Global Pharmacovigilance and Epidemiology, Sanofi Genzyme, Cambridge, MA, USA
[d] Clinical Development, Rare Diseases Group, Sanofi Genzyme, 500 Kendall Street, Cambridge, MA 02142, USA

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ABSTRACT

Enzyme replacement therapy (ERT) with laronidase has an important role in the treatment of patients with mucopolysaccharidosis type I (MPS I). Laronidase is safe and has demonstrated effectiveness in terms of stabilizing or improving conventional clinical and laboratory markers of the disease. However, like most ERTs, laronidase produces an anti-drug IgG antibody response in more than 90% of patients during the first few months of treatment. Preclinical data from the MPS I canine model suggest that anti-drug antibodies (ADA) impair enzyme uptake in target tissues. In patients, the effects on tissue glycosaminoglycan (GAG) clearance are difficult to assess directly but data from clinical studies have suggested an association between ADA and both a reduced pharmacodynamic response and hypersensitivity reactions. This comprehensive meta-analysis of pooled data from patients in three clinical studies of laronidase (including one study with an extension) was undertaken to provide a more robust assessment of the relationship between the ADA response to laronidase, clinical and laboratory markers of MPS I, and hypersensitivity reactions. The meta-analysis demonstrated an inverse relationship between the ADA response and the percent reduction in urinary GAG (uGAG) levels. However, no relationships between the ADA response and changes in percent predicted forced vital capacity and six-minute walk test were seen. The study also re-assayed stored serum samples from the original trials with a novel method to determine the inhibitory effect of ADA. Patients with higher ADA exposure over time were found to have higher inhibition of enzyme uptake into cells. High ADA exposure can result in a commensurate level of enzyme uptake inhibition that decreases the pharmacodynamic effect of the exogenously administered therapeutic enzyme, but with no clear effect on clinical efficacy.

1. Introduction

Mucopolysaccharidosis type I (MPS I) is one of several lysosomal storage diseases for which enzyme replacement therapy (ERT) is safe and effective [15]. MPS I is a clinical spectrum of disease that encompasses severe (Hurler syndrome) and attenuated (Hurler-Scheie and Scheie syndromes) forms without clear delineation. In clinical trials, intravenously administered recombinant human α-L-iduronidase (laronidase/Aldurazyme®, EC 3.2.1.76) demonstrated clinical benefit (improved pulmonary function and walking ability) while lowering markers of glycosaminoglycan (GAG) storage (liver volume and urinary GAG [uGAG] level) in patients with MPS I disease. As laronidase does not cross the blood-brain barrier, it is used to treat the non-neurological symptoms of MPS I, including patients with Hurler and Hurler-Scheie syndromes, and Scheie syndrome with moderate-to-severe symptoms. For Hurler patients younger than two years of age and developmental quotients above 70, hematopoietic stem cell transplantation (HSCT) is considered the standard of care [9]. Based on data from the MPS I Registry, laronidase has been used as an adjunctive therapy in the peri-transplant period in over 90% of cases since 2007, to improve the clinical status of patients prior to HSCT and to reduce GAG storage prior to engraftment [4].

Most ERTs produce an anti-drug antibody (ADA) response, which in some cases can reduce efficacy or lead to hypersensitivity reactions

Abbreviations: % Predicted FVC, percent of predicted normal forced vital capacity; 6MWT, six-minute walk test; ADA, anti-drug antibody; AE, adverse events; AUC/time, area under the curve over time (reflects a weighted average of exposure over a period from baseline through a specific timepoint – see Section 2.4); GAG, glycosaminoglycan; IV, intravenous; RIP, radioimmunoprecipitation; uGAG, urinary glycosaminoglycan; ULN, upper limit of normal.

* Corresponding author.
E-mail addresses: yong.xue@genzyme.com (Y. Xue), susan.richards@genzyme.com (S.M. Richards), asif.mahmood@genzyme.com (A. Mahmood), gerald.cox@genzyme.com (G.F. Cox).

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[1,19]. In clinical trials of MPS I, more than 90% of treated patients developed IgG antibodies to laronidase during the first few months of treatment [21]. (Hereafter, anti-drug IgG antibodies will be referred to as ADA and anti-drug IgE antibodies will be referred to as IgE ADA.) In these studies, higher ADA titers were associated with less uGAG reduction, despite overall evidence of clinical benefit [3,22].

Development of an immune response has the potential to impair the desired biological effects of the therapeutic enzyme through several means, including altered enzyme targeting, increased enzyme turnover, and/or inhibition of enzyme activity [1]. Data from a canine model of MPS I suggest that ADA may impair enzyme uptake in tissues, leading to less tissue GAG clearance and greater uGAG excretion [5]. In patients, the effects of ADA on tissue GAG clearance are difficult to assess since biopsies from clinically relevant organs and tissues cannot readily be performed. However, data from clinical studies of laronidase have suggested that the reduction in uGAG excretion is more robust in patients with low ADA titers, while patients with higher titers had more variable reductions in uGAG clearance [22]. This apparent correlation between the ADA response and uGAG clearance has been consistently observed in multiple clinical studies, despite differences in the patient population, dose and duration of treatment, and method for determination of ADA titer [7,21,22]. The impact of the ADA response on safety and efficacy of ERT with laronidase continues to be investigated.

This comprehensive, systematic meta-analysis of pooled data from patients in three clinical studies of laronidase (including one study with an extension) was undertaken to provide a more definitive assessment of the relationship between laronidase ERT, the ADA response, clinical outcome and laboratory measurements, and the potential for allergic reactions.

2. Methods

2.1. Studies

The designs of the three studies – ALID-003-99/ALID-006-01 (phase 3 study and long-term extension) [21], ALID-014-02 (under 5 study) [22] and ALID-017-03 (dose optimization study) [7] – are summarized in Table 1. ALID-003-99 was a multicenter, multinational, phase 3 trial of laronidase administered intravenously for 26 weeks in 45 patients, all of whom had attenuated MPS I. ALID-006-01 was a 182-week extension study of all 45 patients who completed ALID-003-99. The two trials were treated as one study for this meta-analysis. ALID-014-02 was a 52-week, phase 2 trial to assess the safety, efficacy, and pharmacokinetics of laronidase in 20 patients with MPS I who were five years of age or younger at enrollment and who were not being considered for hematopoietic stem cell transplantation. ALID-017-03 was a phase 4, 26-week dose-optimization study, undertaken to determine whether alternative dosing regimens could further reduce lysosomal storage in 33 patients across the range of MPS I phenotypes. All patients enrolled and treated in all four studies had a confirmed deficiency of iduronidase activity and a clinical diagnosis of MPS I, and had not been previously treated with laronidase. Written informed consent, and assent if applicable, was obtained for all patients in all studies.

2.2. Patient population

This meta-analysis involved the pooling of data from 73 MPS I clinical trial patients who received at least one IV infusion of laronidase at the labeled dose (0.58 mg/kg of body weight per week [qw] [100 U/kg qw]). Where patients received multiple dose levels, only data from the time that they received the labeled dose were included. The number of patients from each study that was used in the meta-analysis is shown in Table 1, as are the demographics of the pooled population which spanned all three MPS I phenotypes. Results of genotyping for α-L-iduronidase mutations were available for 34 patients, either from the clinical study database or from the global MPS I Registry.

2.3. Seroconversion and anti-drug antibody titer

Periodic testing for ADA was performed for all patients in all four studies. ADA in patient serum samples was initially screened by enzyme-linked immunosorbent assay (ELISA) and reactive samples were confirmed by radioimmunoprecipitation (RIP) assay. Once a sample was confirmed to be positive, ADA levels were quantified either by absorbance at 450 nm (expressed as optical density [OD] units/μL) in study ALID-003-99/ALID-006-01, or by endpoint titration (expressed in titer) in studies ALID-014-02 and ALID-017-03. Titer represents the last serial dilution in which the signal is positive, whereas a single OD unit/μL can be associated with a limited range of titers. Therefore, stored serum samples from study ALID-003-99/ALID-006-01 were re-

Table 1
Summary of clinical trials included in meta-analysis.

Study #	ALID-003-99	ALID-006-01[a]	ALID-014-02	ALID-017-03
Phase	3	3	2	4
Randomized	X			X
Double blind, placebo-controlled	X			
Open-label		X	X	X
Treatment duration (wks)	26	182[b]	52	26
Age in years, mean (range)	15.8 (6.3–43.3)		3.0 (0.7–5.1)	8.6 (2.9–17.2)
Total number treated[c]	45[d]		20	33
# analyzed in meta-analysis	45		20[e]	8[f]
Gender, M/F	22/23		12/8	3/5
Race, W/B/A/O/unknown	37/0/2/2/4		18/1/0/1/0	4/1/0/2/1
Phenotype (H/H-S/S)	0/38 (84%)/7 (16%)		16 (80%)/4 (20%)/0	2 (25%)/4 (50%)/2 (25%)

[a] ALID-003-99 and ALID-006-01 were conducted under separate study protocols but are considered to be one study for the purpose of the meta-analysis.
[b] For patients randomized to active treatment in ALID-003-99, the total period of laronidase treatment was up to 208 weeks. Patients randomized to placebo in ALID-003-99 received the first infusion of laronidase in ALID-006-01.
[c] Includes only those enrolled patients who received at least 1 infusion of laronidase (at any dose). For ALID-017-03, the number in this row include some patients whose data were not included in the meta-analysis.
[d] In ALID-003-99, 22 patients were randomized to laronidase and 23 patients were randomized to placebo. All 45 patients subsequently enrolled in ALID-006-01 and received laronidase in that study.
[e] Four of the 20 patients had uGAG levels >200 μg/mg creatinine at week 22 and received a subsequent dose increase to 1.2 mg/kg per week (qw) (200 U/kg qw) between week 26 and week 30. Data for these 4 patients were analyzed only through week 26.
[f] Patients in this study were randomized to receive IV infusions of laronidase at a dose of 0.58 mg/kg qw, 1.2 mg/kg qw, 1.2 mg/kg every other week (qow), or 1.8 mg/kg qow (300 U/kg qow). Eight of the 33 patients treated in the study received laronidase at the labeled dose of 0.58 mg/kg qw.