Treatment Outcomes with Pegzilarginase Compared with Standard of Care for Patients with Arginase 1 Deficiency

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Background and objectives

Overview of Arginase 1 Deficiency (ARG1-D)

Background

Progressive, life-threatening inherited metabolic disease characterized by persistent high levels of arginine and arginine metabolites[1,2]

Key manifestations (**spasticity, seizures, and cognitive impairment**) typically begin in **early childhood** and can lead to significant morbidity and early mortality[2-4]

Managed with dietary protein restriction, which has inadequate effectiveness and rarely reduces arginine to recommended levels of less than 200 µmol/L[2,3,5]

Patients may also be treated with ammonia scavengers to decrease **risk of hyperammonemia**[5]

An open-label, multi-center **Phase 1/2 study of pegzilarginase** enrolled 16 patients diagnosed with ARG1-D; safety and efficacy data were available for 13 patients at 56 weeks of follow-up[6]

Objectives

The objectives of this study were to conduct a systematic literature review of the clinical burden and outcomes for the standard of care in patients with ARG1-D and to compare them to the data from the Phase 1/2 study on pegzilarginase, a novel recombinant human arginase enzyme therapy

1. Carvalho DR, et al. *Gene.* 2012;509:124–130; 2. Carvalho DR, et al. *Pediatr Neurol.* 2012;46:369–374; 3. Amayreh W, et al. *Dev Med Child Neurol*. 2014;56:1021–1024; 4. Bakhiet M, et al. *Medicine (Baltimore).* 2018;97:e10780; 5. Haberle J, et al. *Orphanet J Rare Dis.* 2012;7:32; 6. Diaz GA, et al. European Journal of Neurology. 2020;27 (Supplement 1):1271.

Methods

Systematic literature review (SLR) to identify case reports of patients with ARG1-D

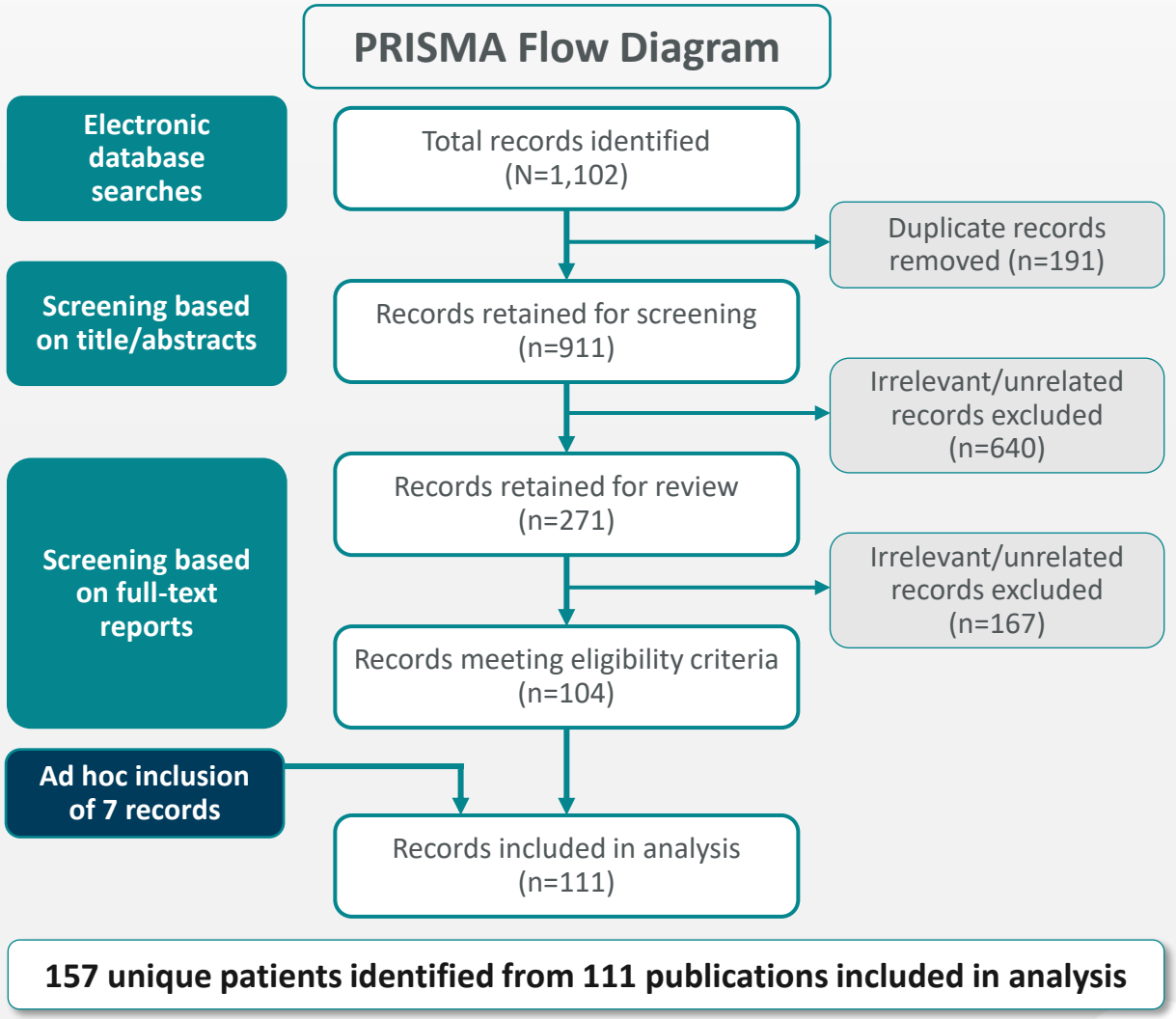
This SLR was conducted using rigorous methods according to

- **The Cochrane Handbook for Systematic Reviews of Interventions**[1]
- **Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement**[2]
- **The US Food and Drug Administration meta-analysis draft guidance for industry**[3]

A detailed, prospectively registered protocol is available in PROSPERO: registration ID CRD42020212142

High level methodology included –

- Comprehensive literature searches to identify eligible case reports
- Study selection by two independent reviewers in two stages: 1. abstract review and 2. full-text review
- Data collection and risk of bias assessments by two independent reviewers
- Descriptive data analysis with quality checks



1. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Available from www.training.cochrane.org/handbook. Published 2020. 2. J Clin Epidemiol. 2009;62(10):1006-1012. 3. Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry [DRAFT GUIDANCE], 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/meta-analyses-randomized-controlled-clinical-trials-evaluate-safety-human-drugs-or-biological.

Baseline characteristics

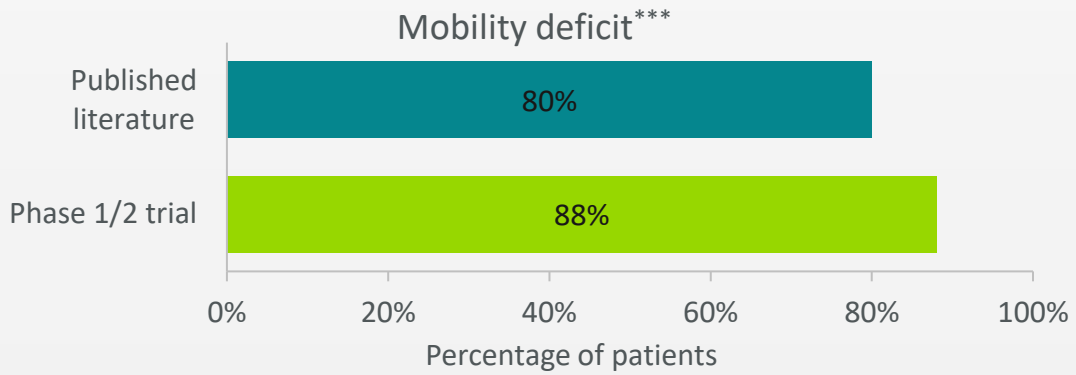
Comparison of patients in the published literature and Phase 1/2 trial*

Patient characteristics

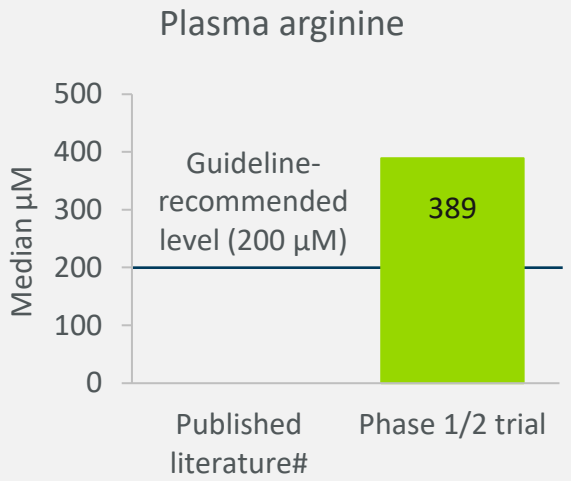
	Published literature* (n=157)	Phase 1/2 trial (n=16)
Confirmed diagnosis**	81%	100%
Age, median (range)	8 years (0 to 60)	15 years (5 to 31)
Female, %	43%	69%
Ethnicity, Hispanic or Latino, %	20%	56%
Spasticity, %	69%	75%
Developmental delay, %	37%	56%
History of seizures, %	50%	25%

Note: These published cases may or may not be the best source of information to describe the ARG1-D patient population as other databases (e.g., Urea Cycle Disorders Consortium and real-real-world data) may report different numbers and results.

Clinical presentation



Laboratory parameters



*Data for the published literature is based on what information was explicitly reported; Note: lack of reporting of a given variable is not confirmation that the characteristic was not present; **Method of diagnosis either mutation in the arginase 1 gene or deficiency in red blood cell activity; ***In the published literature, mobility deficit defined by authors as it includes spasticity, uncontrolled movements, problems walking, talking, or swallowing. In Phase 1/2 trial, mobility deficit defined by one or more of three mobility assessments (6MWT, GMFM-D, and GMFM-E); #Plasma arginine levels were not consistently reported at baseline in the published literature; 1. Haberle J, et al. *JIMD*. 2019;42(6):1192-1230.

Results and conclusions

Treatment outcomes comparing standard of care with a Phase 1/2 trial of pegzilarginase

Measure	Published literature (standard of care)	Phase 1/2 trial (data at week 56)
Baseline Treatment	Standard of care that include: • Protein-restricted diet • Amino acid supplementation • Nitrogen scavenger use	Pegzilarginase in addition to standard of care.
Improvements in Plasma Arginine		
Treatment Guidelines *(<200 µM)*	• 18% of patients achieved at some time point	• 100% of patients achieved within 56 weeks
Normal Range *(40-115 µM)*	• N/A	• 77% of patients achieved within 56 weeks
Improvements in Clinical Outcomes		
Overall Clinical Response	• 28% of patients with some level of motor function improvement*	• 85% of patients with minimal clinically important difference (MCID) in mobility. Pegzilarginase used in addition to existing standard of care**
Safety and Tolerability		
Safety and Tolerability	• Adverse events and safety findings poorly described in case reports	• Favorable safety profile • Most TEAEs were mild

Conclusions

- ✓ Elevated plasma arginine levels were marked and motor deficits common among patients with ARG1-D in both the published literature and pegzilarginase trial at baseline
- ✓ Marked reduction in plasma arginine levels in the phase 1/2 trial compared with standard of care suggests that pegzilarginase could fulfill an unmet treatment need for patients with ARG1-D
- ✓ Reduction in plasma arginine levels were accompanied by improvements in mobility outcomes as assessed by one or more of three quantitative mobility assessments in the phase 1/2 trial
- ✓ The majority of studies in the published literature did not provide information on treatment-related clinical outcomes
- ✓ Pegzilarginase demonstrated a favorable safety profile

Limitations

Disparate and inconsistent reporting of data in the published literature limits statistical comparisons; a lack of reporting of a given intervention or outcomes is not confirmation that the intervention was not employed, or that the outcome was not achieved

Some level of improvement was reported in mobility in approximately one-quarter of patients after initiation of standard therapy in published reports compared to an incremental minimal clinically important difference in mobility seen in 85% of patients after the addition of pegzilarginase to existing standard therapy.

*Only 40 cases reported motor function outcomes (11 patients out of 40 reported improvement); **Clinical responder defined by clinically meaningful achievement in one or more of three mobility assessments (6MWT, GMFM-D, and GMFM-E); 1. Haberle J, et al. JIMD. 2019;42(6):1192-1230; 2. Luneburg N, et al. J Nutr. 2011:41(12):2186-2190.

TEAE: Treatment Emergent Adverse Event