Clinical Features of Arginase 1 Deficiency: Review of Global Literature

Poster P-57

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Introduction

- ARG1-D is a severe, autosomal recessive metabolic disease with progressive, heterogeneous manifestations including spasticity, impaired mobility, developmental delay, and early mortality
- Control of plasma arginine levels is inadequate and problematic with current disease management
- Persistent high plasma arginine levels are believed to be the key driver of disease progression (Waisbren, 2018)
- Hyperammonemia is less problematic than in other UCDs (De Deyn 1997)
- Meaningful quantitative deficits in adaptive behavior, using standardized clinical measures, have recently been described in ARG1-D patients (Waisbren, 2018)
- Pegzilarginase is an engineered, pegylated human arginase 1 currently in development for ARG1-D

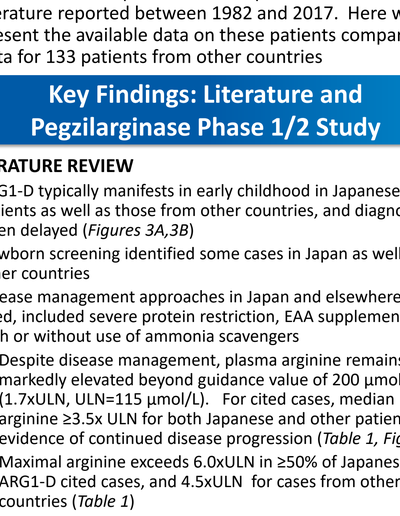


Figure 1. Metabolic Impact of ARG1-D

Methods

- 140 unique patient case reports (English language) from 1965 to current date have been reviewed and the data summarized
- Cases were considered unique based on assessment of the following parameters: country of origin, gender, current calculated age, age at diagnosis, age at presentation or age at onset where available
- We identified 7 Japanese ARG1-D patient cases in the literature reported between 1982 and 2017. Here we present the available data on these patients compared to data for 133 patients from other countries

Key Findings: Literature and Pegzilarginase Phase 1/2 Study

LITERATURE REVIEW

- ARG1-D typically manifests in early childhood in Japanese patients as well as those from other countries, and diagnosis is often delayed (*Figures 3A,3B*)
- Newborn screening identified some cases in Japan as well as in other countries
- Disease management approaches in Japan and elsewhere, where cited, included severe protein restriction, EAA supplementation, with or without use of ammonia scavengers
  - Despite disease management, plasma arginine remains markedly elevated beyond guidance value of 200 µmol/L (1.7xULN, ULN=115 µmol/L). For cited cases, median arginine ≥3.5x ULN for both Japanese and other patients with evidence of continued disease progression (*Table 1, Figure 2*)
  - Maximal arginine exceeds 6.0xULN in ≥50% of Japanese ARG1-D cited cases, and 4.5xULN for cases from other countries (*Table 1*)
  - GVA and ArgA were also elevated in patients (ULN in normal controls 0.2 µmol/L for both, *Table 1*)
- This analysis demonstrates significant morbidity and early mortality in ARG1-D Japanese cited cases consistent with other countries (*Table 1, Figure 3A*)
- Common manifestations include lower limb spasticity, cognitive impairment, failure to thrive, developmental delay, and hyperammonemic episodes
- All patients denoted with upper limb spasticity also had lower limb spasticity
- Biochemical hyperammonemia (≥1 prior value ≥100 µmol/L) noted in 6/6 (100%) cited cases for Japanese patients and 49/ 86 (57%) cited cases for other patients

PEGZILARGINASE PHASE 1/2 STUDY

- 100% (6/6 patients) who completed part 2 achieved consistent levels of reduced arginine (within guideline target; Figure 5)
- Arginine reduction was accompanied by marked and sustained decreases in plasma guanidino compounds (data not shown)
- 67% (4/6 patients) had improvement beyond the MCID in mobility and/or adaptive behavior after only 8 weeks of repeat dosing with pegzilarginase (Figure 6)
  - 33% of assessments favorably exceeded MCID, while none unfavorably exceeded MCID
  - 1/3 of adaptive behavior (ABAS-3) assessments favorably exceeded MCID with 2/3 trending toward improvement at 8 weeks

Disclosures Andreas Schulze and George Diaz are consultants to Aeglea BioTherapeutics, Inc.

James Wooldridge, Gillian Bubb, and Stephen Eckert are employees of, and have an equity interest in, Aeglea BioTherapeutics, Inc. Kiran Patki is a former employee of Aeglea BioTherapeutics, Inc.

Literature Review Results

Table 1. Patient Characteristics and Clinical Biochemical Findings

Parameter	Japan All Results	Other Countries Median (Q1 to Q3) [N]
PATIENT CHARACTERISTICS		
Age at time of report (years)	1, 13, 21, 25, 37	11.0 (5.0 TO 20.0) [98]
Gender: n/N (%) male	5 / 6 (83%)	68 / 119 (57%)
CLINICAL BIOCHEMICAL FINDINGS		
Arginine (µmol/L)		
Prior (max known)	534 604 682 778 1115 1131	563 (433 to 701) [106]
Under disease mgmt.	456 450 702 234	399 (290 to 478) [29]
GVA (µmol/L)	2.94, 3.50	4.83 (3.39 to 6.85) [25]
ArgA (µmol/L)	2.14, 2.20	3.12 (2.30 to 4.04) [25]

Figure 2. Reported Clinical Disease Manifestations

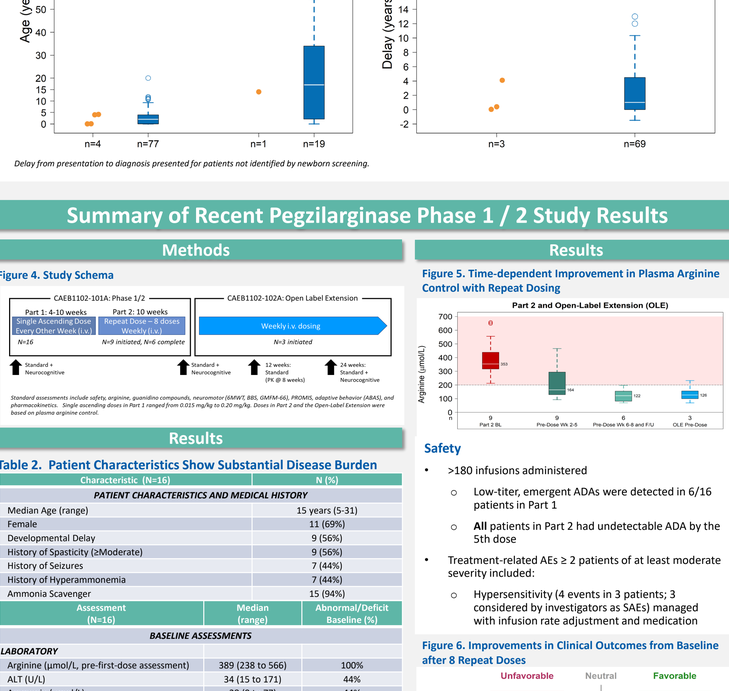
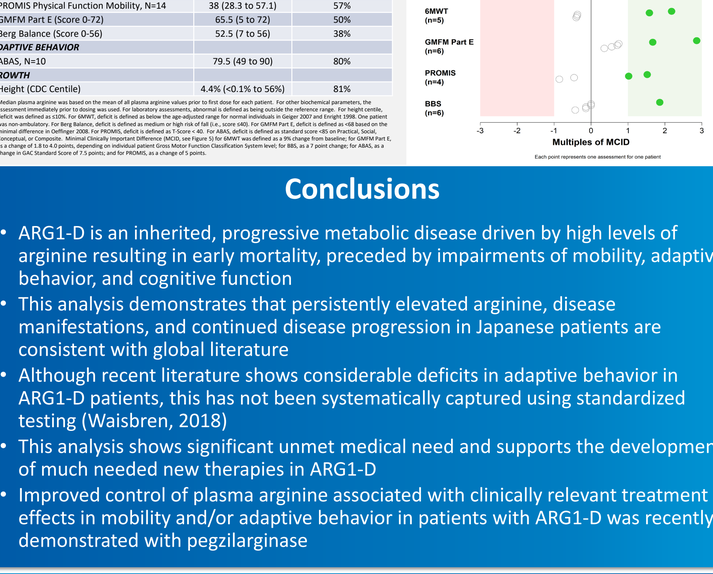


Figure 3. Age at Presentation, Delay to Diagnosis, Mortality



Delay from presentation to diagnosis presented for patients not identified by newborn screening.

Summary of Recent Pegzilarginase Phase 1 / 2 Study Results

Methods

Figure 4. Study Schema



Standard assessments include safety, arginine, guanidino compounds, neuromotor (6MWT, BBS, GMFM-66), PROMIS, adaptive behavior (ABAS), and pharmacokinetics. Single ascending doses in Part 1 ranged from 0.015 mg/kg to 0.20 mg/kg. Doses in Part 2 and the Open-Label Extension were based on plasma arginine control.

Results

Table 2. Patient Characteristics Show Substantial Disease Burden

Characteristic (N=16)	N (%)
PATIENT CHARACTERISTICS AND MEDICAL HISTORY	
Median Age (range)	15 years (5-31)
Female	11 (69%)
Developmental Delay	9 (56%)
History of Spasticity (≥Moderate)	9 (56%)
History of Seizures	7 (44%)
History of Hyperammonemia	7 (44%)
Ammonia Scavenger	15 (94%)

Assessment (N=16)	Median (range)	Abnormal/Deficit Baseline (%)
BASELINE ASSESSMENTS		
LABORATORY		
Arginine (µmol/L, pre-first-dose assessment)	389 (238 to 566)	100%
ALT (U/L)	34 (15 to 171)	44%
Ammonia (µmol/L)	38 (9 to 77)	44%
MOBILITY		
6MWT (m), N=15	349 (102 to 602)	87%
PROMIS Physical Function Mobility, N=14	38 (28.3 to 57.1)	57%
GMFM Part E (Score 0-72)	65.5 (5 to 72)	50%
Berg Balance (Score 0-56)	52.5 (7 to 56)	38%
ADAPTIVE BEHAVIOR		
ABAS, N=10	79.5 (49 to 90)	80%
GROWTH		
Height (CDC Centile)	4.4% (<0.1% to 56%)	81%

Median plasma arginine was based on the mean of all plasma arginine values prior to first dose for each patient. For other biochemical parameters, the assessment immediately prior to dosing was used. For laboratory assessments, abnormal is defined as being outside the reference range. For height centile, deficit was defined as ≤10%. For 6MWT, deficit is defined as below the age-adjusted range for normal individuals in Geiger 2007 and Enright 1998. One patient was non-ambulatory. For Berg Balance, deficit is defined as medium or high risk of fall (i.e., score ≤40). For GMFM Part E, deficit is defined as <58 based on the minimal difference in Oeffinger 2008. For PROMIS, deficit is defined as T-Score < 40. For ABAS, deficit is defined as standard score <85 on Practical, Social, Conceptual, or Composite. Minimal Clinically Important Difference (MCID, see Figure 5) for 6MWT was defined as a 9% change from baseline; for GMFM Part E, as a change of 1.8 to 4.0 points, depending on individual patient Gross Motor Function Classification System level; for BBS, as a 7 point change; for ABAS, as a change in GAC Standard Score of 7.5 points; and for PROMIS, as a change of 5 points.

Results

Figure 5. Time-dependent Improvement in Plasma Arginine Control with Repeat Dosing



Safety

- >180 infusions administered
  - Low-titer, emergent ADAs were detected in 6/16 patients in Part 1
  - **All** patients in Part 2 had undetectable ADA by the 5th dose
- Treatment-related AEs ≥ 2 patients of at least moderate severity included:
  - Hypersensitivity (4 events in 3 patients; 3 considered by investigators as SAEs) managed with infusion rate adjustment and medication

Figure 6. Improvements in Clinical Outcomes from Baseline after 8 Repeat Doses

Conclusions

- ARG1-D is an inherited, progressive metabolic disease driven by high levels of arginine resulting in early mortality, preceded by impairments of mobility, adaptive behavior, and cognitive function
- This analysis demonstrates that persistently elevated arginine, disease manifestations, and continued disease progression in Japanese patients are consistent with global literature
- Although recent literature shows considerable deficits in adaptive behavior in ARG1-D patients, this has not been systematically captured using standardized testing (Waisbren, 2018)
- This analysis shows significant unmet medical need and supports the development of much needed new therapies in ARG1-D
- Improved control of plasma arginine associated with clinically relevant treatment effects in mobility and/or adaptive behavior in patients with ARG1-D was recently demonstrated with pegzilarginase

References: Japanese Patients: [Segawa, Y et al, 2011 Brain & Dev 33: 45-48. Yoshino, M et al, 1982 Urea cycle disease, eds A Lowenthal, A. Mori & B Marescau p121-125. New York: Plenum Press. Haraguchi Y et al 1990 J. Clin. Invest 86: 347-350]; [Mizutani, N et al 1983 Brain Dev 5: 555-563, Mizutani, N et al 1987 Tohoku J exp Med 153: 197-205, Mizutani, N et al 1987 Tohoku J. exp. Med 151: 301-307], Uchino, T et al 1992 Am J Hum Genet 51: 1406-1412; Sakiyama, T et al 1984 Tohoku J exp Med 142: 239-248; Iijima, S 2011 J Med Cases 2 (2) 67-70; Kido J et al 2017 J Inherit Metab Dis 35 (5) 777-785
Other countries patients: Guanidino Compounds in Biology and Medicine II, De Deyn 1997; PMID:27038030; PMID: 22633632; PMID: 9378897; PMID: 24814679; PMID: 24907092; PMID: 28892883; PMID: 23559324; PMID: 21229317; PMID: 12640389; PMID: 19381865; PMID: 9106111; PMID: 21802329; PMID: 15565656; PMID: 24258525; PMID: 29443755; PMID: 21310339; PMID: 22964440; PMID: 14605507; PMID: 19562505; PMID: 29768370; PMID: 20025860; PMID: 26169240; PMID: 29961243; PMID: 29961498

Abbreviations: ARG1-D=Arginase 1 Deficiency, UCD=Urea Cycle Disorder. ASS1=Argininosuccinate synthase 1. ASL=Argininosuccinate lyase. GVA=α-keto-δ-guanidinovaleric acid, ArgA=argininic acid. NAA=N-acetyl-arginine. GAA= guanidinoacetic acid. H_2O=Water. EAA=Essential Amino Acid(s). ULN=Upper Limit of Normal. NOS=Not Otherwise Specified. Q1=First quartile (25th percentile). Q3=3rd Quartile (75th percentile). ALT=alanine aminotransferase. 6WMT=6-Minute Walk Test. PROMIS=Patient-Reported Outcome Information System. GMFM=Gross Motor Function Measure. ABAS=Adaptive Behavior Assessment Scale. GAC=General Adaptive Composite. BBS=Berg Balance Scale. ADA=Anti-Drug Antibody. AE=Adverse Event. SAE=Serious AE. CDC=United States Centers for Disease Control. PK=Pharmacokinetic(s). BL=Baseline. F/U=Follow-up. Wk=Week.