Improved tolerability following enzyme replacement therapy switch to pegunigalsidase alfa: a case series from two centers of the expanded access program

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Introduction

- IRRs are a frequent side effect of ERTs,[1] varying from mild to severe,[2] and may impact patient quality of life[3]
  - IRRs have been associated with ERT immunogenicity and tend to occur predominantly in the first year after ERT initiation but can also persist over time in some patients on long-term ERT[4–6]
- The efficacy and safety of pegunigalsidase alfa[7,8] has been extensively studied in > 140 patients with FD[4,9–13]
  - In BALANCE,[13] the only head-to-head Phase 3 trial in FD, patients were randomly assigned to receive pegunigalsidase alfa or agalsidase beta for 2 years. Despite a similar proportion of patients reporting IRRs in both groups, IRR rates were significantly lower among patients who switched to pegunigalsidase alfa compared with those who remained on agalsidase beta (0.5 vs 3.9 events per 100 infusions, $p < 0.0001$)
- To further understand the effect of switching to pegunigalsidase alfa in patients with a history of poor tolerability to agalsidase beta, we assessed patients from two centers participating in the EAP (NCT04552691) of pegunigalsidase alfa
- The EAP was established to provide access to pegunigalsidase alfa before its US approval (May 2023) for patients who cannot be adequately treated with other approved FD therapies and were unable to participate in ongoing US clinical trials

Objective

- To describe the experience of patients who had switched from agalsidase beta to pegunigalsidase alfa owing to tolerability issues at two participating EAP centers

Methods

- In the EAP, patients received pegunigalsidase alfa (1 mg/kg body weight) as an intravenous infusion every 2 weeks
  - Prior to the EAP, agalsidase beta was administered (~1 mg/kg body weight, intravenously)
- If premedication was used during previous ERT administration, it was initially continued for 3 months; afterwards, gradual discontinuation of premedications could be attempted at investigator's discretion based on patient tolerability
- Results reported are based on medical records and review of the EAP until transfer to commercially available pegunigalsidase alfa or data cut-off date of March 14, 2024

Results

Patient overview

- Four adults with FD (3 male, 1 female) were enrolled at the two US EAP centers between May 25, 2021 and April 14, 2023 owing to poor tolerability of agalsidase beta
- Each patient had > 3 years of continuous prior treatment with agalsidase beta (**Table 1**)
  - 1 male had 11 years of ERT experience, including treatment with agalsidase alfa for 2 years
- 3 patients (2 male, 1 female) have since ended their participation in the EAP (between September 2023 and January 2024) and have transitioned to commercial pegunigalsidase alfa

Limitations

- This analysis of 4 patient cases from two US sites is based on a small patient population. Additional tolerability data from patients switching ERT to pegunigalsidase alfa is needed to further characterize the generalizability of these findings

Table 1. Patient characteristics

	Adult patients (N = 4)
Sex	Male; Female
Time since FD diagnosis	5–10 years; 11–20 years
Duration of previous AB exposure	< 5 years; 5–10 years; 11–20 years
Number of PA Infusions	≤ 30; 31–60; ≥ 61
Duration of PA exposure	≤ 12 months; 13–24 months; ≥ 25 months

Summary of outcomes following switch to pegunigalsidase alfa

- The female patient reported stable energy levels throughout the dosing period and currently receives 60-minute infusions without premedication
- All males reduced or discontinued premedication with few to no IRRs
  - 3/3 discontinued corticosteroids
  - 2/3 achieved reduced infusion duration
- No patients experienced pegunigalsidase alfa-related severe adverse events
  - Mild IRRs were reported but are now controlled with adequate premedications (swollen lip/hives experienced by 1 male patient, and mild chilling/nausea and anxiety experienced by 1 male patient)
  - 1 male experienced several non-related severe adverse events, including 1 episode of MI

Patient profiles

Patient 1: in 20s

Medical history	• Neuropathic pain • GI symptoms (nausea, vomiting, GE reflux, diarrhea) • Fatigue • Episodes of light headedness • Myopia/hyperopia/astigmatism • Feet/lower leg swelling • Irregular menses • Raynaud's phenomenon • Joint pain/stiffness • Anxiety • Migraines • Oral ulcers • Palpitations • Seizures
Reason(s) for EAP enrollment	Worsening fatigue prior to AB infusions

	Agalsidase beta	Pegunigalsidase alfa
ADA status	⊖	⊕ EAP baseline; ⊖ Subsequent test(s)
Infusion duration	Start: 4.5 hours → Reduced to ~1.5 hours within 3 months	Start: 3 hours per EAP protocol → Reduced and maintained at 1 hour within 4 months
Tolerability of ERT and premedications	• Cycling pattern of breakthrough symptoms between infusions in which significant fatigue/body ache/GI symptoms are experienced a few days prior to infusion, with patient feeling re-energized 2–3 days post-infusion • History of mouth sores 2–3 days after ERT infusion • No premedications used	• Improved fatigue and stable energy between infusions • No worsening of disease • Mouth sores reduced (unclear if due to PA or preventative methods) • No premedications used

Patient 2: in late teens

Medical history	• FD-related hypohidrosis • Neuropathic pain • Fatigue • Heat intolerance • Angiokeratomas
Reason(s) for EAP enrollment	Multiple IRRs to AB

	Agalsidase beta	Pegunigalsidase alfa
ADA status	⊕	⊕ EAP baseline; ⊕ All subsequent test(s)
Infusion duration	Start: 4 hours → Reduced to 2 hours over 6–12 months → Increased to 3 hours owing to IRR recurrence after ~10 years of infusion, then maintained at 2.5 hours (with corticosteroid in premedications)	Start: 3 hours per EAP protocol → Maintained at 3 hours (without corticosteroid in premedications)
Tolerability of ERT and premedications	• IRRs (nausea, rigors, vomiting) required premedications (up to 4, including intermittent use of corticosteroids) • Prednisone was stopped, but IRR recurrence required reinitiation. Infusions were reduced to 2.5 hours, with continued random experience of milder IRRs • Experienced post-infusion fatigue (switched diphenhydramine to cetirizine to decrease fatigue)	• 1 mild IRR (swollen lip/hives) in first 12 months when premedication taken too far in advance of scheduled infusion to adequately control potential IRRs • Discontinued half of premedications including corticosteroid • No other IRRs and no fatigue post-infusion

Patient 3: in 20s

Medical history	• End-stage renal disease; disease on hemodialysis since 2020 • Anemia due to chronic kidney disease • Hypertension secondary to other renal disorders • Secondary hyperparathyroidism of renal origin • Proteinuria • Dyspepsia • Neuropathic pain • Hyperphosphatemia • Diarrhea • Abdominal pain • Cramping
Reason(s) for EAP enrollment	Multiple IRRs to AB

	Agalsidase beta	Pegunigalsidase alfa
ADA status	⊕	⊕ EAP baseline; ⊕ Subsequent test(s)
Infusion duration	Start: ~3 hours → Gradually increased to 4–5 hours owing to IRRs (with corticosteroid in premedications) → Infusion duration remained stable after titration of premedications	Start: 3 hours per EAP protocol → Reduced and maintained at 1 hour within 1 year (without corticosteroids)
Tolerability of ERT and premedications	• Multiple IRRs on AB requiring extensive premedications (up to 9 medications including corticosteroids) • Persisting GI distress (diarrhea, abdominal pain, and cramping) • History of mouth sores after ERT infusion	• Initial infusions maintained infusion rate and premedications as with prior ERT, per EAP protocol • Premedications withdrawn sequentially and eventually eliminated • No IRRs or mouth sores experienced and no premedications used • Improved GI symptoms and pain (unclear if due to PA or new symptomatic treatment)

Patient 4: in 50s

Medical history	• Coronary artery disease • Stroke • 5 episodes of MI 4 on AB, 1 on PA • Mitral valve regurgitation • Chronic kidney failure (hemodialysis started in 2018, transition to peritoneal dialysis in 2020) • Transient ischemic attacks • Renal cell carcinoma requiring nephrectomy • Hypertension • Avascular necrosis of hip • Bipolar affective disorder • Myopia and retinopathy • Asthma • Chronic nausea and vomiting • Pancreatitis • Meningitis • Acroparesthesias
Reason(s) for EAP enrollment	Multiple IRRs to AB; FD progression, worsening GI symptoms. Multiple MIs, transient ischemic attack, began dialysis, and had worsening claudication

	Agalsidase beta	Pegunigalsidase alfa
ADA status	⊕	⊕ EAP baseline; ⊕ All subsequent test(s)
Infusion duration	Start: 4.5 hours → Reduced to 2.5 hours within 3.5 months (with corticosteroid in premedications) → IRRs required intermittent increases in infusion duration	Start: 3 hours per EAP protocol → Reduced and maintained at 1–1.5 hours within 6 months (without corticosteroid in premedications)
Tolerability of ERT and premedications	• Multiple IRRs (eg, rigors, chilling, nausea) requiring extensive premedication use (up to 7, including corticosteroids) • Famotidine used until minimum infusion duration of 2.5 hours was achieved	• IRRs eliminated while premedications were being discontinued; however, had IRRs (mild chilling/nausea, anxiety) recur a year after premedication stopped; required reinitiation of fexofenadine • No other subsequent IRRs reported

Conclusions

- Based on insights from this case series and from post hoc analyses of clinical trials of pegunigalsidase alfa (see poster by Longo et al.*), switching from agalsidase beta to pegunigalsidase alfa treatment may offer the benefit of lower IRR incidence, reduced infusion duration, and lower premedication burden for some patients with poor tolerability to agalsidase beta
- Findings from a single female patient indicate improvement in symptom breakthrough prior to next ERT infusion upon switch to pegunigalsidase alfa; however, these observations need to be confirmed in a larger population
- Full results from the EAP will provide additional insights on the tolerability of pegunigalsidase alfa outside of clinical trials

*Poster #213: Lower Rate of Infusion-Related Reactions in Patients with Fabry Disease After Switching from Agalsidase Beta to Pegunigalsidase Alfa

Abbreviations

AB, agalsidase beta; ADA, antidrug antibody; EAP, Expanded Access Program; ERT, enzyme replacement therapy; FD, Fabry disease; GE, gastroesophageal; GI, gastrointestinal; IRR, infusion-related reaction; MI, myocardial infarction; PA, pegunigalsidase alfa; SD, standard deviation.

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Acknowledgments: The authors thank the patients and their families. The expanded access program was sponsored by Chiesi, USA, Inc. Medical writing support was provided by Leanne M. Low, PhD, of Oxford PharmaGenesis Inc., Newtown, PA, USA, and funded by Chiesi, USA, Inc.

Disclosures: MDH received speaker-related fees from Protalix and has been, or is currently, involved in clinical trials with Avrobio, Idorsia, Protalix, Sangamo, and Sanofi (no direct funding is received for these trials as they are institution directed). **JAB** receives research support from Avrobio, BioMarin Pharmaceutical, Chiesi Farmaceutici, Denali Therapeutics, Idorsia Pharmaceuticals, Pfizer, Protalix Biotherapeutics, Sangamo Therapeutics, Sanofi, Takeda, and Travere Therapeutics; has received a speaker honorarium from the Fabry Support and Information Group; and has participated in advisory boards for Chiesi USA, Mirum Pharmaceuticals, Sanofi, and Takeda. **DL** is a member of the North American Fabry Registry Board and cofounder of ThinkGenetic Inc.; has grant funding from Amicus Therapeutics and Sanofi-Genzyme and Sanofi-Genzyme; has received honoraria for consulting agreements with Amicus Therapeutics, Chiesi, Protalix, Sanofi-Genzyme, Spark Therapeutics, and Takeda.

This poster was originally presented at the 8th Fabry Disease Update, June 2–4, 2024.