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Lower rate of infusion-related reactions in patients with Fabry disease after switching from agalsidase beta to pegunigalsidase alfa

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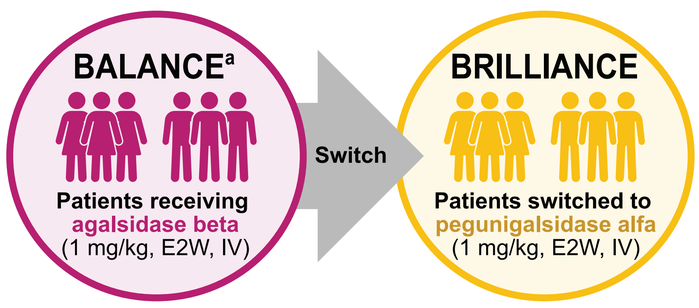
Introduction

- The efficacy and safety of pegunigalsidase alfa[1,2] has been extensively studied in > 140 patients with Fabry disease (FD)[3–8]
- Infusion-related reactions (IRRs) are a limitation of enzyme replacement therapies (ERTs),[9] and can vary from mild to life-threatening[10]
- IRRs are associated with ERT immunogenicity and tend to occur predominantly in the first year after initiating an ERT, but can also persist over time in some patients on long-term ERT[5,11,12]
- PEGylation of pegunigalsidase alfa could reduce immune response, including IRR incidence, by modulating immunogenicity via epitope masking[13] or by enabling sustained drug exposure[14,15]
- BALANCE is the only head-to-head, double-blind, Phase 3 trial in patients with FD, comparing agalsidase beta and pegunigalsidase alfa[8]
  - Despite a similar proportion of patients reporting IRRs in both groups, lower IRR frequency was observed among patients who switched to pegunigalsidase alfa compared with agalsidase beta (0.5 vs 3.9 events per 100 infusions, $p < 0.0001$)
  - IRRs within 24 hours were experienced by 8/25 patients treated with agalsidase beta, and per protocol, patients required premedication or decreased infusion rate
- Patients who completed BALANCE could continue or switch to treatment with pegunigalsidase alfa in the open-label extension study, BRILLIANCE

Objective

- To assess if switching from agalsidase beta to pegunigalsidase alfa in the open-label extension study BRILLIANCE resulted in a change in IRR frequency for patients who had IRRs on agalsidase beta during BALANCE

Methods



[a]IRR history with agalsidase beta prior to BALANCE enrollment was not collected; therefore, a comparison of IRR rate in patients that switched to pegunigalsidase alfa treatment in BALANCE was not possible.

- Patients who had ≥ 1 IRR while receiving agalsidase beta in BALANCE (NCT02795676) for 2 years and subsequently switched to pegunigalsidase alfa in BRILLANCE (NCT03566017; data cut-off date: April 2, 2024) were included
- IRR incidence (during and up to 24 hours post-infusion), IRR frequency (rate adjusted to 100 infusions), and premedication use were evaluated

Results

Patient demographics and baseline characteristics

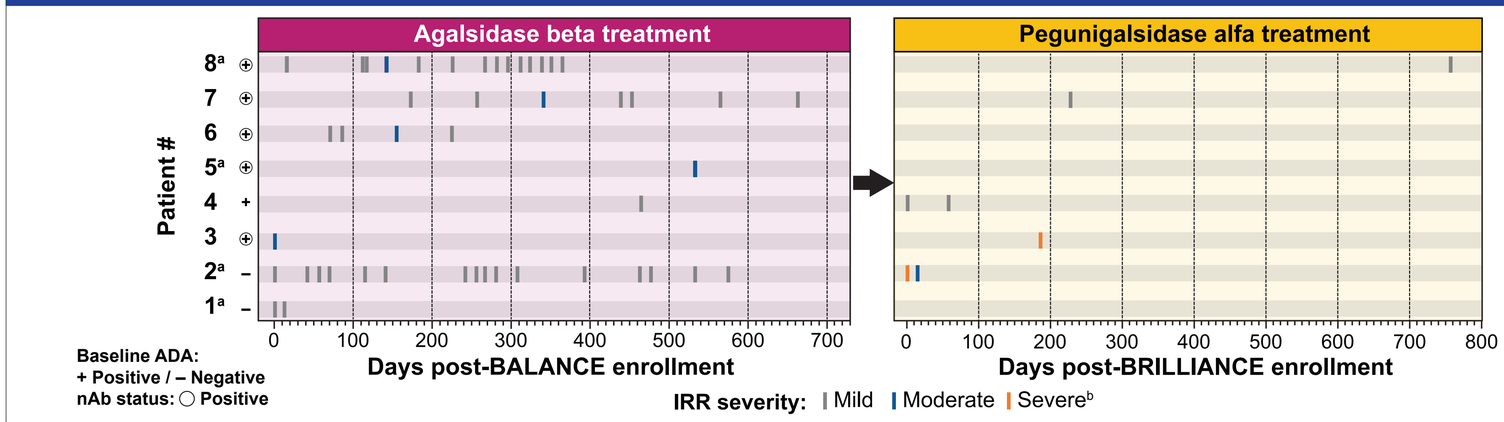
- 8/25 patients taking agalsidase beta in BALANCE experienced ≥ 1 IRR event despite having previously been exposed to agalsidase beta for an average of 7.8 years (range: 4.1, 14.0 years) prior to study enrollment (**Table 1**)

Table 1. Patient demographics

	Patients (n = 8)
Age, years	
Mean (SD)	44.0 (7.5)
Minimum, maximum	35, 54
Sex, n	
Male, Female	7, 1
Duration of last AB treatment, years[a]	
Mean (SD)	7.8 (3.4)
Minimum, maximum	4.1, 14.0
Number of AB infusions during BALANCE	
Mean (SD)	53.3 (1.6)
Minimum, maximum	52, 57
Number of PA infusions during BRILLIANCE	
Mean (SD)	94.6 (18.3)
Minimum, maximum	64, 119

[a]Last treatment refers to patients who had AB treatment before BALANCE enrollment.

Figure 1. IRRs over time



[a]Patients experienced ≥ 2 IRR (ie, different symptoms that may vary in length of time) during the same day (Patient 1: days 1, 13; Patient 2: days 57, 141; Patient 5: day 533; Patient 8: days 16, 114, 142, 226, and 282). The highest severity is reported; [b]Grades 3–4 severity in the clinical database were merged under the term 'severe' in the safety database.

Infusion-related reactions

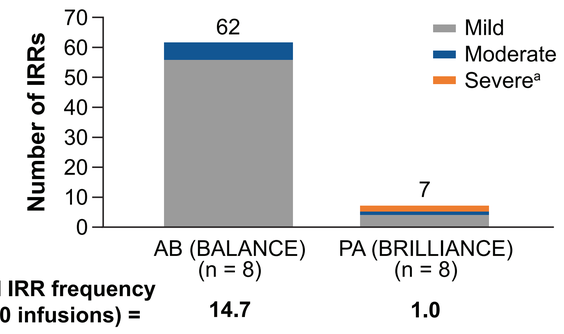
- Lower number of IRR total events and frequency were observed in the 8 patients post-switch to pegunigalsidase alfa compared with agalsidase beta (**Figure 1 and 2**)
  - 62 IRRs were experienced by 8 patients with agalsidase beta during BALANCE
  - Post-switch to pegunigalsidase alfa, 3/8 patients (**#1, #5, and #6**; all male) received a mean of 95 infusions and experienced no IRRs. The remaining 5 patients (mean: 95 pegunigalsidase alfa infusions) had a total of 7 IRRs (mean IRR frequency: 1.6 per 100 infusions)
  - Overall IRR frequency was 14.7 (agalsidase beta during BALANCE) vs 1.0 (pegunigalsidase alfa during BRILLIANCE)
  - At BALANCE baseline, 6/8 patients (**#3–8**) were positive for IgG anti-drug antibodies (ADAs), 5 of whom had neutralizing ADAs (IgG titer range: 422–22956; **Figure 1**)
  - 3 patients (**#2, #7, and #8**) were suspected of having a hypersensitivity reaction during BALANCE and received additional IgE ADA testing (at time of event and retroactively testing the sample collected at BALANCE screening). 2/3 (**#7 and #8**) and 3/3 patients had ≥ 1 positive IgE test to agalsidase beta and pegunigalsidase alfa, respectively
- 55/62 and 4/7 of IRR events reported with agalsidase beta and pegunigalsidase alfa, respectively, were mild. 2 severe IRRs were reported with pegunigalsidase alfa (**Figure 2**)
  - **Patient #2** (female) experienced a severe IRR (anaphylactic reaction) on day 1 of pegunigalsidase alfa treatment resulting in reduced infusion rate; this IRR was not previously experienced with agalsidase beta treatment, and did not recur in subsequent pegunigalsidase alfa infusions despite patient being IgE positive to study drug (**Table 2**). This patient later experienced a moderate IRR (throat itching/intermittent cough) on day 15
  - **Patient #3** had a severe IRR (chills) on day 186 with pegunigalsidase alfa treatment and had no other subsequent IRRs
- All events resolved, and none led to study discontinuation

Table 2. IRR events during ERT

	Agalsidase beta (BALANCE)	Pegunigalsidase alfa (BRILLIANCE)
Total number of IRR events, n	62	7
Preferred terms, n		
Pruritus[a]	25	1
Infusion-related reaction	5[b]	2[c]
Pain[d]	5	0
Erythema	3	0
Dermatitis allergic	3	0
Rash[e]	3	1
Limb discomfort	2	0
Chest discomfort	2	0
Malaise	2	0
Hypersensitivity	1	1
Chills	1	1[f]
Blood pressure increased	1	0
Feeling hot	1	0
Fatigue	1	0
Paresthesia	1	0
Heart rate increased	1	0
Urticaria	1	0
Throat irritation	1	0
Diarrhea	1	0
Nausea	1	0
Headache	1	0
Anaphylactic reaction	0	1[g]

[a]Includes pruritic rash and oral pruritus; [b]Descriptions include respiratory distress/rigors, wheezing/trouble breathing, wheezing/cough/shortness of breath, hives/wheezing/tingling, and hives/itching; [c]Descriptions include throat itching/intermittent cough and fatigue day after infusion; [d]Includes non-cardiac chest pain and upper abdominal pain; [e]Includes papule; [f]Severe IRR experienced by Patient #3; [g]Severe IRR described as facial and lip swelling, throat tightness, shortness of breath, and nausea, prompted immediate administration of epinephrine, saline, steroids, and diphenhydramine in Patient #2.

Figure 2. IRR events during ERT

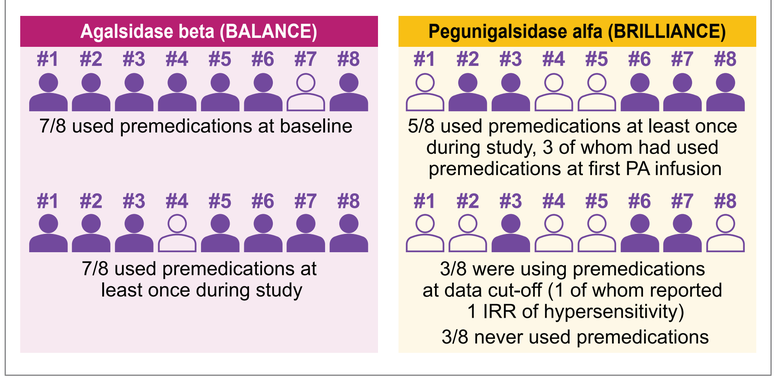


[a]Grades 3–4 severity in the clinical database were merged under the term 'severe' in the safety database.

Infusion premedication

- Overall, premedication use by patients with IRRs was lower after switching to pegunigalsidase alfa compared with agalsidase beta

Figure 3. Premedication use



Conclusions

- These data suggest that some patients with a history of long-term treatment with agalsidase beta and repeated IRRs may be less likely to experience IRRs or have reduced need for premedications after switching to pegunigalsidase alfa
  - IRR frequency was ~15–fold lower after switching to pegunigalsidase alfa
  - IRR number was ~9–fold lower after switching to pegunigalsidase alfa
  - While the likelihood of anaphylaxis is rare, healthcare providers should be aware of the potential risk and monitor for symptoms closely after ERT initiation
  - Premedication use was lower after switching to pegunigalsidase alfa, with 5/8 patients not using premedications at the data cut-off date, 2 of whom had never taken premedications during pegunigalsidase alfa treatment despite having taken it at least once with agalsidase beta

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Abbreviations
AB, agalsidase beta; ADA, anti-drug antibody; E2W, every 2 weeks; ERT, enzyme replacement therapy; FD, Fabry disease; IRR, infusion-related reaction; IV, intravenous; nAb, neutralizing antibody; PA, pegunigalsidase alfa; SD, standard deviation.

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