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Evaluating the relationship between infusion-related reactions and anti-drug antibody status: Results from 111 patients with Fabry disease treated with pegunigalsidase alfa

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Introduction

- Infusion-related reactions (IRRs) are a known possible side effect of enzyme replacement therapies (ERTs), with their severity ranging from mild to life-threatening[1,2]
- IRRs tend to occur predominantly in the first year after initiating ERT; however, in some patients receiving long-term treatment, these reactions may persist[3-4]
- The mechanism underlying IRRs is not fully understood, but it can be associated with ERT immunogenicity, among other factors including mutation type and patient characteristics
- PEGylation of pegunigalsidase alfa may potentially reduce its immunogenicity by masking enzyme epitopes and/or decreasing anti-drug antibody (ADA) binding affinity, which may in turn lower the incidence of IRRs[5,6]
- In the Phase 3 BALANCE study, the rate of IRRs per 100 infusions was lower among patients who had switched to pegunigalsidase alfa than patients who remained on agalsidase beta, despite similar proportions of patients experiencing IRRs in both groups[5]
  - While patients with ADAs had a higher risk of IRRs with both ERTs, the IRR rate was lower with pegunigalsidase alfa than agalsidase beta in ADA-positive patients as well.[5] However, the specific characteristics of these ADAs and other contributing factors that influence the risk of developing IRRs remain unclear

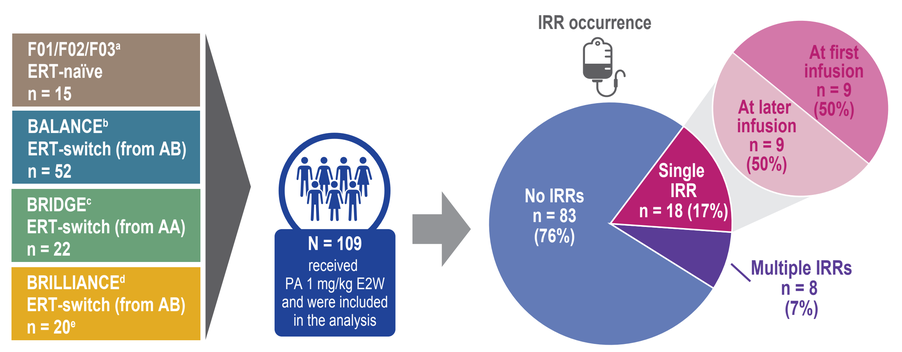
Objective

- To explore the association between occurrences of IRRs and IgG ADAs in patients with Fabry disease who received pegunigalsidase alfa 1 mg/kg every 2 weeks (E2W) in clinical trials

Methods

- This analysis included patients (N = 111) pooled from the pegunigalsidase alfa clinical trial program (**Figure 1**) receiving pegunigalsidase alfa at 1 mg/kg E2W
- IRRs were defined as treatment-emergent adverse events occurring during or up to 2 hours after an infusion, with causality assessed as definitely, probably, or possibly treatment related, excluding events such as injection-site reactions which were considered to be procedure related[5]
- Only IRRs that occurred during treatment with pegunigalsidase alfa 1 mg/kg E2W were included in this analysis. 2/111 patients were excluded as they experienced IRRs during a prior different dose of PA but not while receiving 1 mg/kg dose
- Patients (n = 109) were grouped based on the infusions in which IRRs occurred: no IRR, single IRR at the first infusion, single IRR at any later infusion, multiple IRRs
- Immunoglobulin G (IgG) ADA titer was evaluated at baseline and during pegunigalsidase alfa treatment
  - IgG ADA titer category was based on quartiles of all observed titers, and thresholds were defined as: low, < 1100; medium-low, 1100–5600; medium-high, 5600–14,000; high, > 14,000

Figure 1. Schematic of the pooled analysis from pegunigalsidase alfa trials



[a]F01 and F02 were both open-label, dose-ranging, Phase1/2 studies, with F02 being a 9-month extension of F01 (3 months). F02 was further extended into F03 with treatment duration of up to 60 months before continuation into BRILLIANCE.
[b]PA treatment duration was 24 months in BALANCE before continuation into BRILLIANCE.
[c]PA treatment duration was 12 months in BRIDGE before continuation into BRILLIANCE.
[d]BRILLIANCE is an ongoing, open-label, extension study consisting of patients from F03, BALANCE, and BRIDGE, who will continue to receive PA for up to 60 months following termination of the parent studies (cut-off date, July 15, 2021).
[e]Represents patients who received AB in BALANCE and switched to receive PA 1 mg/kg E2W for the first time in BRILLIANCE.
Trials that were pooled in this analysis: F01, NCT01678898; F02, NCT01769001; F03, NCT01981720; BALANCE, NCT02795676; BRIDGE, NCT03018730; BRILLIANCE, NCT03566017.
AA, agalsidase alfa; AB, agalsidase beta; ERT, enzyme replacement therapy; E2W, every 2 weeks; IRR, infusion-related reaction; PA, pegunigalsidase alfa.

Results

Patients

- Of 109 patients, 63.3% (69/109) were male and 36.7% (40/109) were female (**Table 1**)
- Most patients (86.2%, 94/109) had switched ERT (from agalsidase alfa [n = 22] or agalsidase beta [n = 72]), with 13.8% of patients (15/109) being ERT-naïve
- At baseline, 23.9% of patients (26/109) were IgG ADA-positive for pegunigalsidase alfa (**Table 2**)

Infusion-related reactions

- Overall, most patients (76.1%, 83/109) did not experience an IRR (**Table 1**)
- A total of 52 IRRs occurred at a rate of 0.7/100 infusions; most of these (84.6%, 44/52) occurred during the first year of treatment
- Less than a quarter of patients (23.9%, 26/109) experienced at least 1 IRR with pegunigalsidase alfa (**Figure 1**)
  - Of these 26 patients, most (69.2%,18/26) experienced a single IRR (half at first infusion and half at a later infusion), while 30.8% (8/26) experienced multiple IRRs (**Table 1**)
  - Similar proportions of patients (22.7–26.7%) who were ERT-naïve or had switched from agalsidase alfa or agalsidase beta experienced at least 1 IRR
  - Of 4 ERT-naïve patients with IRRs, 3 had multiple IRRs, whereas only 5 of 22 ERT-switch patients with IRRs had multiple IRRs
- Four patients who experienced IRRs discontinued treatment and withdrew from the study after their first (n = 3; 1 ERT-naïve, 2 ERT-switch) or second infusion (n = 1; ERT-switch)
- Proportionately more men than women experienced at least 1 IRR (30.4% [21/69] and 12.5% [5/40], respectively)

IRR occurrence and relationship with IgG ADAs over time

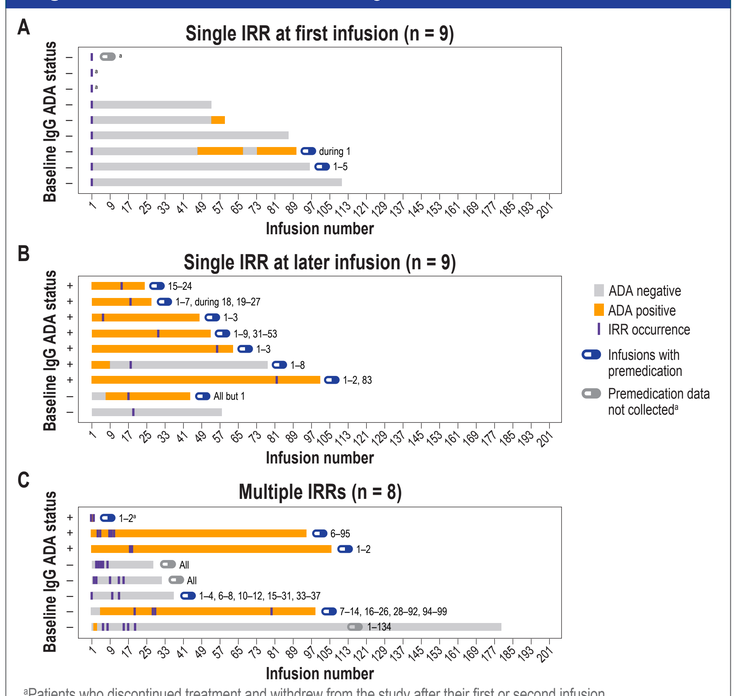
- Proportionately more patients who were IgG ADA+ at baseline experienced at least 1 IRR than patients who were IgG ADA– at baseline (38.5% [10/26] versus 19.3% [16/83]) (**Table 2**)
- All patients (n = 9) who experienced a single IRR at first infusion were baseline IgG ADA–, with 3/9 becoming IgG ADA+ during treatment (**Table 2**)
- Of the 9 patients who experienced a single IRR at later infusions, 7 (77.8%) were IgG ADA+ at baseline and remained IgG ADA+ during treatment
  - Of these, 6 had medium-high or high IgG ADA titers before the IRR occurrence
- Of the 8 patients with multiple IRRs, 3 (37.5%) were IgG ADA+ at baseline and continued to be IgG ADA+ throughout treatment; two of whom reported high IgG ADA titers before IRR occurrence
  - For 3 of the 8 patients (37.5%), IRRs occurred when they were not receiving premedication

Table 1. Baseline patient characteristics stratified by IRR occurrence (N = 109)

	Age, years, mean (SD)	Male, n = 69, n (%)	Female, n = 40, n (%)	ERT-naïve, n = 15, n (%)	ERT-switch from AA, n = 22, n (%)	ERT-switch from AB, n = 72, n (%)	Total number of PA infusions, mean (range)
No IRRs n = 83	43.3 (11.0)	48 (69.6)	35 (87.5)	11 (73.3)	17 (77.3)	55 (76.4)	69.3 (1–134)
≥ 1 IRR n = 26	42.7 (11.8)	21 (30.4)	5 (12.5)	4 (26.7)	5 (22.7)	17 (23.6)	60.6 (1–180)
Single IRR at first infusion n = 9	41.3 (13.2)	7 (10.1)	2 (5.0)	1 (6.7)	2 (9.1)	6 (8.3)	55.3 (1–110)
Single IRR at later infusion n = 9	45.7 (12.1)	9 (13.0)	0 (0.0)	0 (0.0)	1 (4.5)	8 (11.1)	55.1 (24–101)
Multiple IRRs[a] n = 8	40.9 (10.8)	5 (7.2)	3 (7.5)	3 (20.0)	2 (9.1)	3 (4.2)	72.6 (2–180)

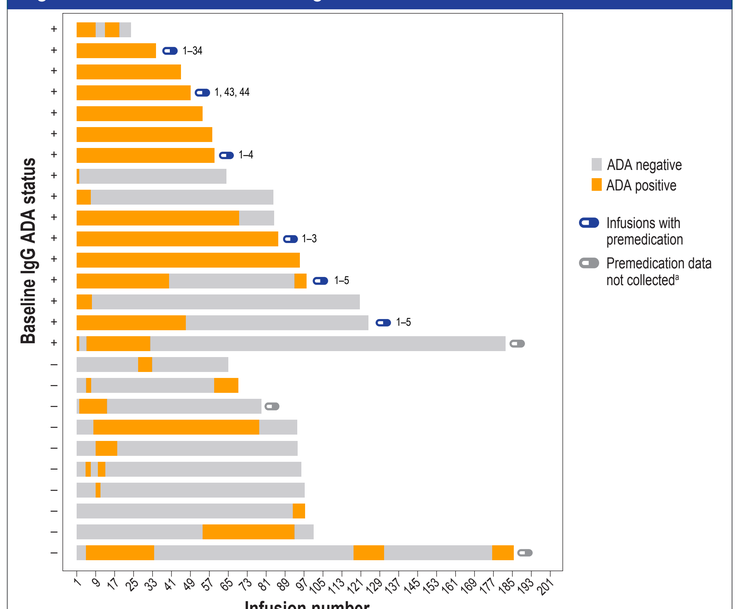
[a]Range, 2–6 IRRs. AA, agalsidase alfa; AB, agalsidase beta; ERT, enzyme replacement therapy; IRR, infusion-related reaction; PA, pegunigalsidase alfa; SD standard deviation.

Figure 2. Occurrence of IRRs and IgG ADA status over time



[a]Patients who discontinued treatment and withdrew from the study after their first or second infusion.
[b]Premedication was received but premedication data were not collected during studies F01/F02/F03.
Each line represents an individual patient, showing IgG ADA status (positive or negative) and IRRs during PA treatment. The presence of IgG ADAs was not evaluated at each infusion and could change between evaluations.
ADA, anti-drug antibody; IgG, immunoglobulin G; IRR, infusion-related reaction; PA, pegunigalsidase alfa.

Figure 3. IgG ADA status over time in patients without IRRs who were IgG ADA+ at least once during treatment[a]



[a]Premedication was received but premedication data were not collected during studies F01/F02/F03.
Each line represents an individual patient, showing IgG ADA status (positive or negative). Only patients who were IgG ADA+ at any time point are shown. The presence of IgG ADAs was not evaluated at each infusion and could change between evaluations.
ADA, anti-drug antibody; IgG, immunoglobulin G; IRR, infusion-related reaction; PA, pegunigalsidase alfa.

Table 2. IgG ADA status at baseline and post-baseline by IRR occurrence

	Baseline IgG ADA status, n (%) n = 109		Post-baseline IgG ADA status, n (%) n = 105[a]		
	Negative, n = 83	Positive, n = 26	Negative, n = 62	Induced, n = 16	Positive, n = 27
No IRRs[b] n = 83	67 (80.7)	16 (61.5)	54 (87.1)	10 (62.5)	17 (63.0)
≥ 1 IRR n = 26	16 (19.3)	10 (38.5)	8 (12.9)	6 (37.5)	10 (37.0)
Single IRR at first infusion[c] n = 9	9 (10.8)	0 (0.0)	4 (6.5)	3 (18.8)	0 (0.0)
Single IRR at later infusion n = 9	2 (2.4)	7 (26.9)	1 (1.6)	1 (6.3)	7 (25.9)
Multiple IRRs[d] n = 8	5 (6.0)	3 (11.5)	3 (4.8)	2 (12.5)	3 (11.1)

[a]ADA status post-baseline is missing for 4 patients (2 with no IRR and 2 with a single IRR at first infusion). [b]One patient terminated after first infusion; one ERT-switch patient had their first pegunigalsidase alfa infusion in BRILLIANCE study, a few weeks prior to the cut-off date for the data sets, and hence no information on ADA post-baseline was available. [c]Two patients discontinued the study after they both had an IRR during the first infusion. [d]Range, 2–6 IRRs.
ADA, anti-drug antibody; ERT, enzyme replacement therapy; IgG, immunoglobulin G; IRR, infusion-related reaction.

IgE ADAs

- Four patients who experienced hypersensitivity reactions were found to be IgE ADA+ (not included in this analysis)
  - Of these, 2 had a single IRR at first infusion and withdrew, 1 had a single IRR at a later infusion, and 1 had multiple IRRs and withdrew

IgG ADAs over time in patients without IRRs

- Among the 83 patients without any IRRs, 16 (19.3%) were IgG ADA+ at baseline and 26 (31.3%) were found to be IgG ADA+ at least once during treatment (**Figure 3**)
  - Most (18/26, 69.2%) had low (n = 9) or medium-low (n = 9) IgG ADA titers ranging from 60–5517
  - 8/26 (30.8%) patients had medium-high (n = 3) or high (n = 5) titers

Limitations

- This analysis was limited to IgG ADAs, but 4 patients with IRRs had IgE ADAs. Analysis including IgE data may have different results
- This analysis did not assess ADA properties that may carry different risk for IRR occurrence, such as IgG subclass or affinity/avidity of binding
- Premedication use may have affected the occurrence of IRRs in ADA+ patients

Conclusions

- In this pooled analysis, most patients receiving pegunigalsidase alfa therapy did not experience IRRs; the majority of patients with IRRs experienced only 1 IRR
- While baseline IgG ADA positivity appears to be a risk factor for IRRs, the presence of pre-existing IgG ADAs alone does not predict the development of IRRs, and there was no clear trend between IgG ADA titer and the occurrence of IRRs
- This analysis suggests that there may be specific IgG ADA characteristics that play a role, among other non-ADA factors, in the risk of experiencing IRRs

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