Post-hoc analysis of pegloticase pivotal trials in chronic refractory gout: relationship between fluctuations in plasma urate levels and acute flares

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Abstract

Objective

To determine factors associated with gout flares in subjects treated with pegloticase.

Methods

Gout flares from two randomised controlled trials comparing pegloticase (8 mg every 2 weeks [q2] or monthly [q4]) versus placebo were analysed. Responders had persistent urate lowering (<6mg/dL) whereas, non-responders had transient urate lowering during the 6-month RCTs. Gout flares (self-reported) were defined as acute joint pain and swelling requiring treatment. Gout flare prophylaxis (colchicine, 0.6 mg once or twice daily, or a non-steroidal anti-inflammatory drug) was initiated 1 week before the first infusion and continued throughout the study. Plasma urate at the time of flare and the change in urate preceding a flare were analysed.

Results

Mean flare rates increased with pegloticase versus placebo during the first 3 months followed by marked reductions during months 4–6. The increase in flares with pegloticase during the first 3 months was most evident (p=0.0006) and the decrease during the second 3 months was least marked (p=0.0006) in subjects receiving monthly pegloticase. Fluctuation in urate levels was highest in monthly responders (p=0.002) and was associated with flare occurrence. Multivariate linear regression analysis indicated the only variables significantly associated with flares were treatment group and absolute change in plasma urate before flares.

Conclusion

Pegloticase treatment increased flares during the first 3 months of treatment in all groups when plasma urate was significantly lowered and was followed by a decline in months 4-6 in patients maintaining a low plasma urate. Flares associated with pegloticase treatment were associated with decreases and fluctuations in plasma urate levels.

Key words

gout, serum urate, inflammatory arthritis

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B.F. Mandell reports consulting and clinical investigator fees of less than $10,000 from Horizon Therapeutics and being a consultant to Takeda, Ironwood Pharmaceuticals and Astra Zeneca;
T.R. Fields reports being an advisor to Takeda, Horizon Therapeutics and Ironwood Pharmaceuticals;
N.L. Edwards reports consulting fees from Astra Zeneca, Horizon Therapeutics, Ironwood Pharmaceuticals, SOBI International;
A.E. Yeo reports contractor fees from Horizon Therapeutics;
P.E. Lipsky reports consulting fees from Horizon Therapeutics.

Introduction

Severe, acute inflammatory arthritis, commonly referred to as a flare, constitutes the most characteristic clinical manifestation in patients with gout (1). Pain, along with redness, warmth, swelling, and stiffness in the affected joint, arises abruptly in gout and disappears when the acute phase of the flare resolves (1). Gout flares are associated with decreased quality of life as well as activity impairment and disability (2-4). Flares have also been associated with increased healthcare resource utilisation and work loss in patients with gout (5, 6).

Persistently elevated serum urate with resultant formation and deposition of monosodium urate (MSU) crystals is pathogenic in gout (7, 8). Reducing serum urate to <6 mg/dL is a well-accepted treatment target (9-13) and the dissolution rate of MSU acid deposits correlates with the degree of lowering of the serum urate level (14, 15).

Despite the evidence that decreasing serum urate therapeutically initially increases the frequency of flares and subsequently decreases their frequency often below baseline levels (16-22), evaluations of the relationship between serum urate and the occurrence of flares have produced various results. A systematic review of the literature and meta-analysis that included results from 10 randomised clinical trials (RCTs) and 3 open-label extensions indicated that a significant relationship between serum urate and gout flares could not be confirmed on the basis of the presented data from the RCTs; but, results from the extension studies indicated that lowering and maintaining serum urate to <6 mg/dL was associated with reduced occurrence of gout flares (23).

Additional analysis suggested that variability in the reporting of both flares and fluctuations in serum urate levels over time likely contributed to the surprisingly weak relationship between these two variables (24). Additionally, a retrospective cohort study using administrative claims data that included information from 18,008 patients, also indicated that serum urate values ≥6 mg/dL were associated with increased flare frequency (25).

Evidence suggests that gout flares might be associated with initial or transient lowering of serum urate. In this regard, a detailed analysis of 41 patients with gout indicated that serum urate was significantly lower during acute flares *versus* the intercritical phase. The percentage change in serum urate at the onset of an attack correlated with levels of C-reactive protein and interleukin-6 (26). The reduction in serum urate during flares is thought to be related to an increase in clearance of urate owing to inflammation (26, 27). These results are consistent with the hypothesis that a decrease in plasma urate level in subjects with gout is associated with an increase in flares because of an altered equilibrium between soluble urate and insoluble MSU crystal deposits (16). This conclusion has recently been supported in a number of large clinical trials of urate lowering therapy, in which an increase in flares was noted during the initial period of urate lowering, whereas more persistent urate lowering ultimately resulted in a decrease in flares, often below that observed in the pretreatment baseline period (17-22). Despite this evidence, there is little consistency in recommendations for preventing and managing gout flares (28).

Pegloticase is a mammalian recombinant uricase conjugated to polyethylene glycol approved for the treatment of chronic gout refractory to conventional oral urate lowering therapy (29). The administration of pegloticase can profoundly lower the plasma urate level (in some patients to <1 mg/dL); in approximately 50% of patients receiving the drug every two weeks a level of <6 mg/dL was maintained over 6 months. Results from the two 6-month RCTs of pegloticase showed that during months 1–3, there was an increase in gout flares in pegloticase-treated subjects vs those receiving placebo (19). The objective of this current study was to identify factors other than acute urate lowering that might be associated with the occurrence of flares in subjects treated with pegloticase for chronic refractory gout. The hypothesis to be tested was that factors other than the initial precipitous decrease in plasma urate might contribute to the increased frequency of gout flares.

Methods

Study design and treatment

This analysis used results from two pivotal RCTs of pegloticase (ClinicalTrials.gov: NCT00325195, NCT01356498). Both RCTs received institutional review board approval for each site and written informed consent and Health Insurance Portability and Accountability Act assurances were completed for each participant prior to enrolment. The baseline demographic characteristics of the subjects enrolled in the RCTs has previously been reported (19, 30). Of the subjects enrolled in the RCTs, only 73% of those receiving pegloticase biweekly had tophi at baseline compared to 76% of subjects receiving pegloticase monthly (30). Both RCTs included two treatment arms: pegloticase (8 mg every 2 weeks [q2] or every 4 weeks [q4]) *vs*. placebo in subjects with chronic refractory gout. All subjects received infusions (either pegloticase or placebo) every two weeks throughout the trial. Plasma urate was determined at baseline, at 2 and 24 hours after the initial infusion, preceding each biweekly infusion, and at 5 additional prespecified time points in both month 3 and month 6. A responder was defined as a subject with plasma urate <6.0 mg/dL ≥80% of the time from the week-9 infusion to just before the week-13 infusion and from the week-21 infusion to the week-25 final study visit (19). Gout flare prophylaxis (colchicine, 0.6 mg once or twice daily, or a non-steroidal anti-inflammatory drug) was initiated one week before the first infusion and continued throughout the study (19). Gout flares were reported according to a protocol definition. Flares were self-reported by subjects in the trial and were defined as acute joint pain and swelling requiring treatment. The occurrence, duration, and severity of flares were reported by subjects at the time of occurrence and confirmed by investigator interview during the course of the trials (19).

Statistical analysis

The chi square test was used in all calculations for analyses of categorical variables. The 2 sample Wilcoxon test was used for analyses of continuous variables. All calculations were carried out with SAS 9.4 (Cary NC).

Multiple linear regression was carried out to model the relationship between the dependent variable, the occurrence of flares, and various independent variables including age, weight, body mass index, treatment group, plasma urate, and change in plasma urate. The final equation that predicted the number of flares was:

Number of flares = 4.54472 + (0.17139 x sum of plasma urate differences) – (0.41593 x Group) – (0.01574 x Age) – (0.00084183 x Weight).

The adjusted r^2 was 0.4304 (p<0.0001).

Ethical approval and consent to participate

The design of the two identical RCTs of pegloticase that provided the data analysed in this study (ClinicalTrials.gov: NCT00325195, NCT01356498) received institutional review board approval for each site and written informed consent and Health Insurance Portability and Accountability Act assurances were completed for each participant prior to enrolment. No additional patient consent was required for the *post-hoc* data analyses undertaken in this study.

Results

This analysis was carried out using results from 36 responders to biweekly pegloticase, 29 responders to monthly pegloticase, 49 biweekly non-responders, 55 monthly non-responders, and 43 subjects who received placebo.

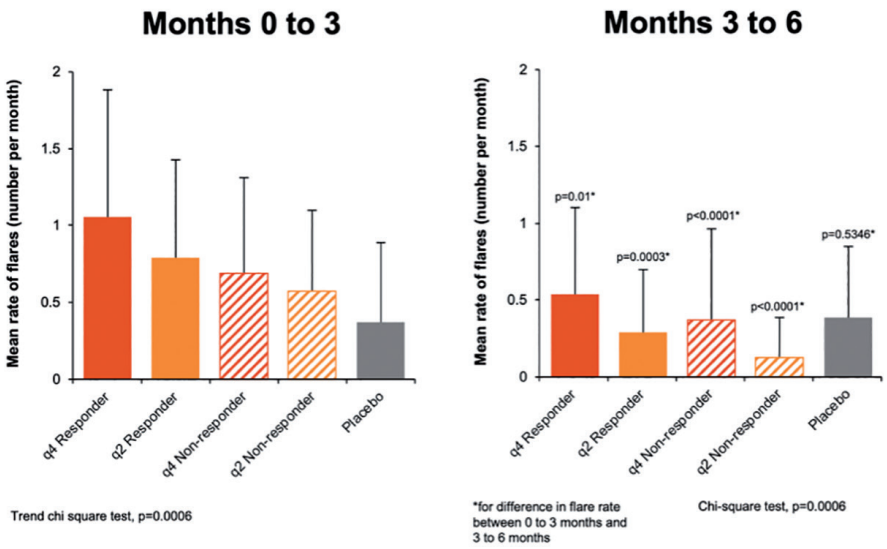

Fig. 1. Flare rates in responders and non-responders to pegloticase. This analysis was carried out using results from 36 responders to q2 pegloticase, 29 responders to q4 pegloticase, 49 q2 non-responders, 55 q4 non-responders, and 43 subjects who received placebo.

Flare rates

There were increases in the mean flare rates in the pegloticase groups vs placebo during the first 3 months of the trial (Fig. 1A). In contrast, there were marked reductions in flare rates in the pegloticase groups, but not in those receiving placebo during months 4–6 (Fig. 1B). The increase in flares in the first 3 months was most evident (p=0.0006) and the decrease during the second 3 months was least marked (p=0.0006) in subjects receiving q4 pegloticase. As there was only a weak correlation between flares and many features of gout (31), the current analysis focused on the relationship with aspects of plasma urate.

Relationship between flares and absolute plasma urate levels

Several analyses were carried out in an effort to understand the higher rate of flares in the responders in the monthly pegloticase arm as compared to responders in the biweekly pegloticase arm. Evaluation of plasma urate levels near the times of flares indicated no significant relationship between plasma urate and the likelihood of reporting a flare. Figure 2 summarises plasma

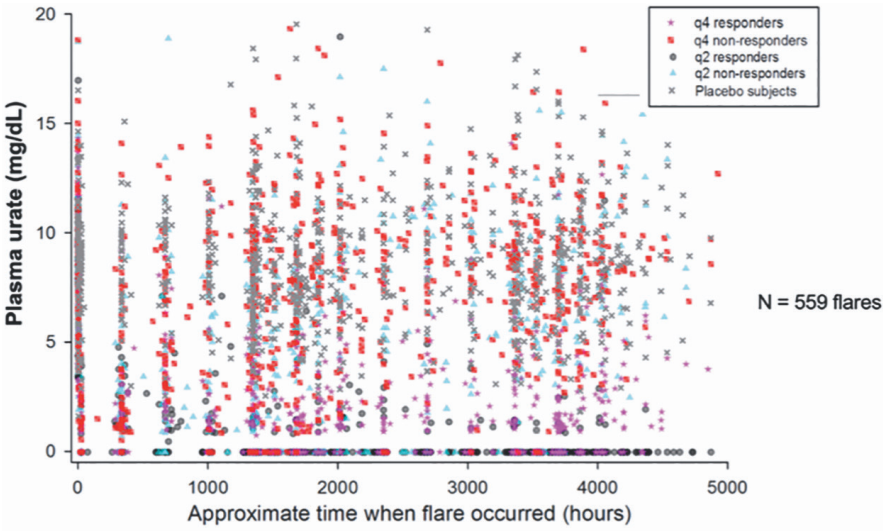

Fig. 2. Flares and plasma urate.

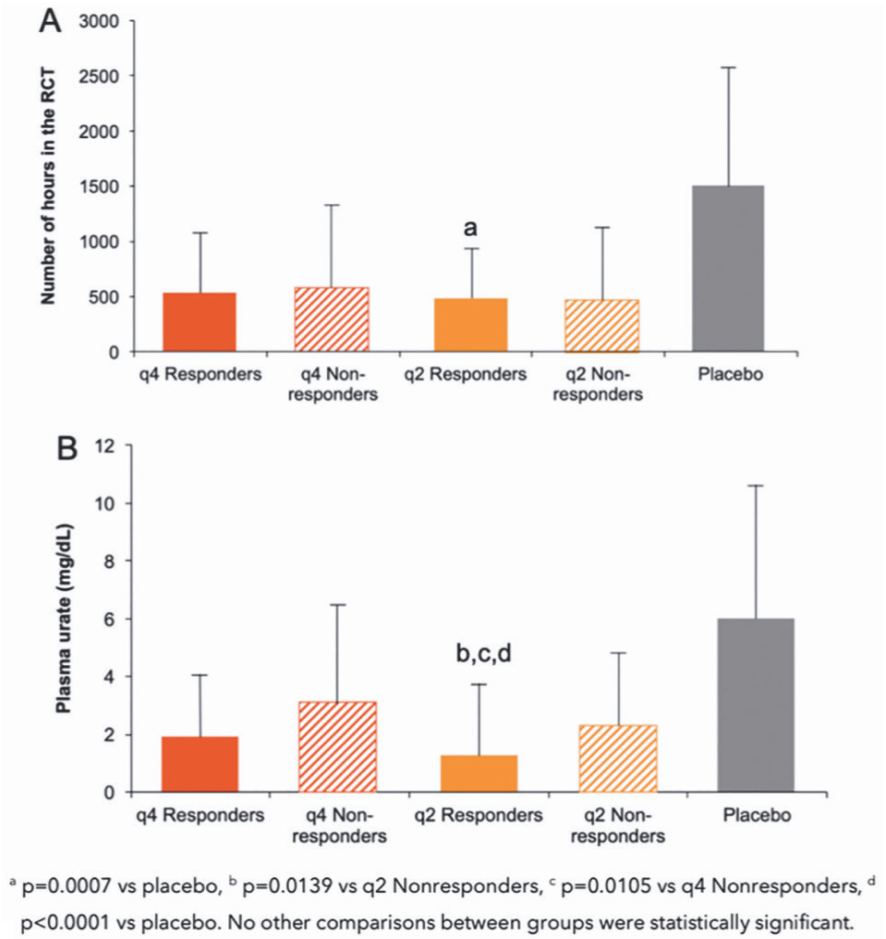

Fig. 3. A: Time to first flare; Plasma urate at the time of first flare. **B**: This analysis was carried out using results from 36 responders to q2 pegloticase, 29 responders to q4 pegloticase, 49 q2 non-responders, 55 q4 non-responders, and 43 subjects who received placebo.

urate levels closest to the times of 559 flares recorded during the two RCTs. No relationship between plasma urate and flares was obvious. Results for all study groups are included in Figure 2.

Time to first flare was also evaluated and results are shown in Figure 3A. In all pegloticase treatment groups the mean time to first flare was approximately 500 hours (21 days), whereas the mean time to first flare in the placebo treated group was approximately 1500 hours (62 days). There were no differences between the q4 responders and any of the other treatment groups with regard to timing of the first flare. Although there were differences among groups with respect to plasma urate levels at the time of the first flare (Fig. 3B), there were no significant differences between values for the q4 responders and the q2 responders, indicating that the difference in the absolute level of plasma urate alone could not explain the difference in flare frequency between these two groups.

Relationship between flares and changes in plasma urate levels

Previous analysis indicated that biweekly pegloticase caused persistently lowered plasma urate in responders, whereas monthly administration resulted in a more saw-toothed pattern, although mean urate remained below 6mg/dL (32). This observation and the fact that the highest flare rate over the first 3 months of treatment occurred in the q4 responders suggested that fluctuations in plasma urate rather than just the absolute levels might be related to the occurrence of flares. Assessment of plasma urate at both 2 weeks and immediately before flares indicated that larger differences between these two values were associated with increased flare occurrence. Absolute changes in urate before flares for q2 responders, q4 responders, and subjects who received placebo are shown for all flares and individual flares in Figures 4A-B, respectively. Analysis of all flares indicated that the absolute changes in urate immediately before flares were significantly greater for q4 responders *versus* those for q2 responders ($p<0.0001$). Similar results were noted when all flares were assessed (Fig. 4B). The association between the change in plasma urate and flare likelihood was confirmed by examining the change in urate before visits that were associated with a flare or not. As shown in Figure 5, a significantly greater change in plasma urate was noted in the 2 weeks bracketing a flare compared to the 2-week periods without a flare in both the q4 ($p=0.0133$)

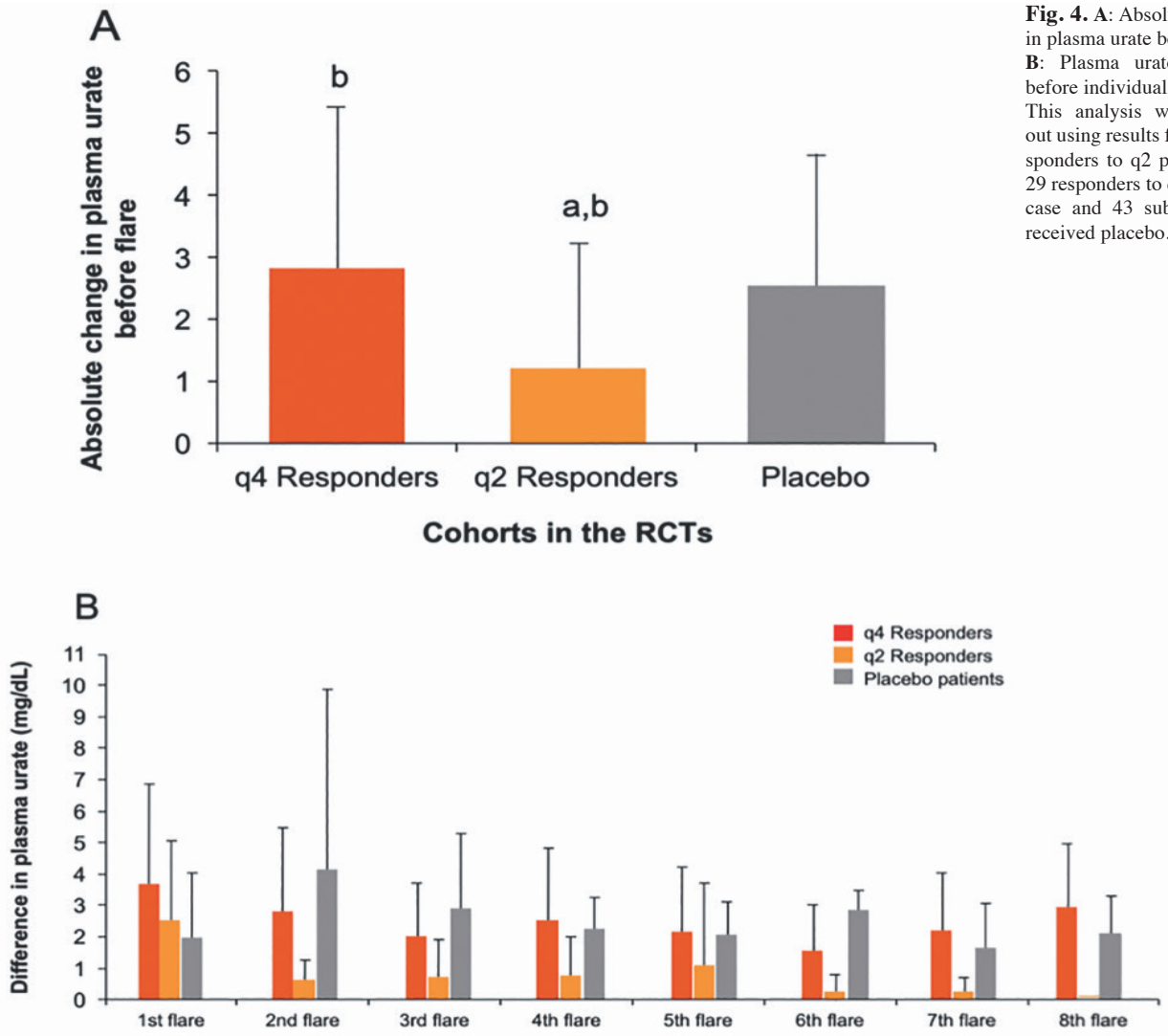

Fig. 4. **A**: Absolute change in plasma urate before flare; **B**: Plasma urate changes before individual flares. This analysis was carried out using results from 36 responders to q2 pegloticase, 29 responders to q4 pegloticase and 43 subjects who received placebo.

[a] p<0.0001 vs q4 Responders and placebo, [b] p<0.0001 for q2 + q4 Responders vs placebo. There was no statistical difference between q4 responders and placebo patients, p=0.8352.

and the q2 (p=0.0068) responders. No significant difference was noted in patients receiving placebo. Multiple linear regression analysis indicated that both change in plasma urate (designated as the sum of plasma urate differences, p<0.0001) and treatment group (q2 *vs*. q4 *vs*. placebo) (p=0.0005) were significantly associated with the likelihood of flares (Table I). This implies that both the initial lowering of plasma urate and changes in the magnitude of urate lowering both contributed to gout flares.

Discussion

The results of this analysis from two RCTs of pegloticase indicated that flares associated with this treatment in subjects with chronic refractory gout were increased in all pegloticase treated subjects. The increase in flares was most pronounced during the first 3 months of treatment when profound lowering of the plasma urate occurs and declined in months 4–6. These results are consistent with those of previous studies which have shown that urate-lowering therapy initially increases and then lowers flare rates in patients with gout and persistent urate lowering (17-22). Results from this analysis also showed that the flare rate was higher in the q4 *versus* q2 responders. Analyses carried out in an effort to understand this difference indicated that there was no significant correlation between plasma urate levels at the time of a flare and the occurrence of an individual flare, but that change in plasma urate over the previous 2-week interval was significantly associated with the increased occurrence of flares in q4 responders (in whom there was more fluctuation of the plasma urate) compared with q2 responders. Multiple regression analysis also indicated that both plasma urate lowering, designated as treatment group assignment, and variability in the magnitude of urate lowering were significantly associated with the likelihood of flares.

It is notable that fluctuations in plasma urate were also noted in placebo treated subjects. However, no difference in the magnitude of change in plasma urate was noted when flares and non-flare periods were compared, suggesting that fluctuations in urate were not in-

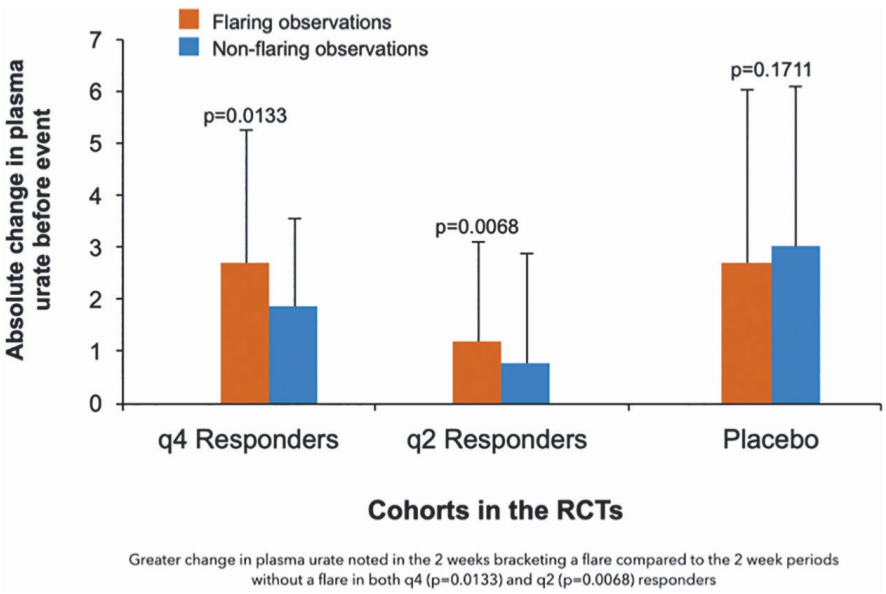

Fig. 5. Greater change in plasma urate precedes flares in pegloticase treated subjects (data for first 8 flares). This analysis was carried out using results from 36 responders to q2 pegloticase, 29 responders to q4 pegloticase and 43 subjects who received placebo.

Table I. Multivariate linear regression model for flares.

Variable	Parameter	*p*-value
Intercept	4.54472	0.0034
Sum of PUA differences	0.17139	<0.0001
Groups: q2, q4, placebo	-0.41593	0.0005
Age (years)	-0.01574	0.2969
Weight (kg)	-0.00084	0.9246

Number of flares: 4.54472 + (0.17139*Sum of PUA differences) - (0.41593*Group) - (0.01574*Age) - (0.00084183*Weight). Overall, the equation is significant, $p<0.0001$. The adjusted r^2 is 0.4304.

volved in initiation of flares in placebo treated subjects, perhaps because all of the changes in urate were occurring in the hyperuricaemic range. Therefore, the effect of the fluctuations in plasma urate may not have altered the solubility of tissue MSU crystals.

The observation that initiation of urate-lowering therapy is associated with increased frequency of flares has been reported previously in patients treated with allopurinol, febuxostat, lesinurad, and pegloticase (4, 16, 17, 19-21, 33-35) and resulted in the recommendation for prophylaxis against flares with either colchicine or a non-steroidal anti-inflammatory drug in patients initiating urate-lowering therapy (10), although there remains inconsistency in the specific recommendations (28). Patients in the current trial were receiving flare prevention therapy and we did not find differences in the flare frequency related to specific treatment regimens. Moreover, all patients, even those receiving placebo, were given glucocorticoids as prophylaxis for infusion reactions, so it is unlikely that difference in steroid usage contributed to flare frequency.

The increase in flares during the initial period of urate-lowering therapy has been attributed to destabilisation of the surface of masses of insoluble urate with release of individual MSU crystals during the initial phase of deposit dissolution with urate-lowering therapy (36). Monosodium urate crystals form in close proximity to each other and immediately become part of a crystalline lattice structure possibly incorporating membrane phospholipids, neutrophil nets and serum proteins (37). The sudden change in microenvironment associated with urate-lowering therapy results in lattice destabilisation and shedding of MSU crystals into the synovial fluid (38). If the shedding is small, the few crystals can be opsonised with ApoE and become non-inflammatory (39). However, if the shedding is large, the shed crystals may interact directly with receptors on inflammatory cells and initiate an inflammatory process (7, 40). If they are opsonised with IgG, this process can be enhanced (41). Bi-weekly pegloticase responders have a low steady state of urate favouring rapid dissolution (15). In contrast, monthly pegloticase responders have a variable state of urate (32) with the low levels favouring dissolution followed by higher levels that would favour incomplete solubilisation with persistence of crystals. This difference may be responsible for the higher flare rate in q4 *versus* q2 responders to pegloticase.

The present results and those from prior evaluations also indicate that it is the period of crystal dissolution that is related to the occurrence of flares. Recognition of this has led to the recommendation that standard urate lowering therapy be initiated at low doses with step wise increments in the expectation that slower decreases in urate with more controlled dissolution might be achieved (42). The possibility that the decrease in urate that occurs during flares owing to changes in urate clearance (26, 27) might further exacerbate the tendency to flare should also be considered. For example, a review of data from 41 patients with acute gouty arthritis during and after attack indicated that serum urate levels were significantly lower during attacks than during intercritical periods; and, that during attacks it dropped to <6 mg/dL in 49% of patients. Reduction in serum urate at the time of flares has also been reported for a cohort of 38 patients with gout (43). Results from 21 of 27 patients with gout who were normouricaemic at the time of a flare, and then followed up, indicated that 81% developed hyperuricaemia at a median of one month after the attack. Additional results from a small cohort of patients studied by Schlesinger *et al*. indicated that declines in serum urate begin before the onset of flares in patients with gout (44). These findings are also consistent with the view that serum urate levels declined at the time of flares and

could contribute to the severity or persistence of the flare, and then returned to higher levels.

This analysis had a potentially important limitation. The definition of flares in the two RCTs was specific, requiring self-reported acute joint pain and swelling requiring treatment verified by the treating physician (19) but somewhat different than a more recently validated definition of gout flare (45). This could be an important consideration since it has been noted that variability in the reporting of flares may increase the difficulty of demonstrating correlations between these events and other variables in patients with gout (24). Although we were not able to determine whether the flares reported in the current study met the validated definition of flare, two of the four proposed criteria (patient defined gout flare, at least one swollen joint) overlapped. Moreover, the definition used in the current study may have been more stringent requiring an event mandating treatment.

Conclusion

This analysis of flares in subjects with chronic refractory gout treated with pegloticase supports two conclusions:

1. this treatment increased flares during the first 3 months of treatment and this was followed by a decline in months 4–6;

2. flares associated with pegloticase treatment were increased most markedly in subjects who experienced greater fluctuations in plasma urate levels. Such fluctuations are much more common with monthly (q4) administration of pegloticase *versus* the currently recommended biweekly treatment regimen.

Availability of data and materials

The data and analytic methods that support the findings of this study are available to qualified investigators by request to the corresponding author.

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