Dissociation Between Clinical Benefit and Persistent Urate Lowering in Patients with Chronic Refractory Gout Treated with Pegloticase

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ABSTRACT. ***Objective.*** To assess clinical benefit in patients with chronic refractory gout who did not meet the protocol-defined criteria of responders to pegloticase.

Methods. This analysis used results from 2 randomized controlled trials (ClinicalTrials.gov: NCT00325195, NCT01356498) to assess the clinical efficacy in responders and nonresponders to treatment (8 mg of pegloticase every 2 weeks). Serum urate was measured before each infusion and the following were recorded: assessment of gout flares, tophus reduction, patient's global assessment (PtGA), tender and swollen joints (TJC and SJC), pain using a 100-mm visual analog scale, and a variety of patient-reported outcomes [Medical Outcomes Study Short Form-36 questionnaire physical component summary score and arthritis-specific health index (ASHI) score].

Results. The analysis included 36 persistent urate responders, 49 nonresponders, and 43 patients who received placebo. Results for both responders and nonresponders indicated significant reduction in tophi and improvements from baseline in PtGA, TJC, SJC, pain, and ASHI. No significant improvements were observed in the patients who received placebo.

Conclusion. Chronic refractory gout patients not achieving protocol-defined persistent urate lowering still achieve significant clinical benefits with pegloticase treatment, suggesting that transient reduction in serum urate may result in sustained clinical benefit. (J Rheumatol First Release November 1 2019; doi:10.3899/jrheum.190161)

Key Indexing Terms:
HYPERURICEMIA GOUT TOPHI

Treatment goals for gout have typically focused on the biochemical response to therapy, i.e., lowering serum urate (SU) to < 6 mg/dl and to even lower levels in selected patients, such as those with extensive crystal deposition[1,2,3]. This is based on the known solubility of urate in aqueous fluid (6.8 mg/dl)[4]. It has been shown that administration of therapy aimed at lowering SU to these levels has clinical benefit[5], including decreasing tender joints, reducing pain, and improving patient's global assessment (PtGA) of disease activity and quality of life (QOL)[6,7,8,9], and this is the standard target for successful treatment. However, it has also been noted that the biochemical treatment goal for SU (< 6 mg/dl), while accepted as a surrogate for clinical outcomes in patients being treated for gout[10] and the primary outcome in many studies of gout treatment[6,11,12,13], may not be closely related to clinical outcomes and that lower levels may result in greater improvement[5,14,15]. For example, results from one small-scale study indicated that profound but transient reductions in urate may result in significant decreases in tophus burden[16]. It is conventionally thought that persistent urate lowering is required to achieve treatment goals[17]. Few studies have examined the possibility that transient urate lowering may have persistent clinical benefit. The reported clinical trials of pegloticase provided the opportunity to examine this question[6].

Pegloticase is a recombinant mammalian uricase, conjugated to polyethylene glycol and approved for the treatment of chronic refractory gout. The pivotal, randomized controlled clinical trials (RCT) for pegloticase were of 6 months' duration and defined responders as patients with plasma urate < 6.0 mg/dl for > 80% of the time during extensive monitoring from both the Week 9 infusion to just before the Week 13 infusion, and from the Week 21 infusion to Week 25 (final visit). Nonresponders did not meet this stringent criterion but had decreases in SU comparable to the responders after the first pegloticase dose, followed by a gradual return to > 6 mg/dl over the next several dose administrations[6]. Mean SU increased to > 6 mg/dl in 6–8 weeks in

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the nonresponders[6,18]. The objective of this analysis was to determine whether these patients with transient serum reductions gained any persistent clinical benefit.

MATERIALS AND METHODS

Design of pegloticase trials. Two replicate randomized, double-blind, placebo-controlled trials were conducted between June 2006 and October 2007 at 56 rheumatology practices in the United States, Canada, and Mexico (ClinicalTrials.gov: NCT00325195, NCT01356498)[6]. Both studies 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 before enrollment. The design and conduct of the studies complied with the Declaration of Helsinki. These studies enrolled patients with chronic gout, along with either allopurinol intolerance or refractoriness, and SU concentration ≥ 8.0 mg/dl. A total of 212 patients participated in the 2 studies, of whom 85 received biweekly pegloticase and 43 received placebo and were evaluated in this analysis. Patients were to receive 12 biweekly intravenous (IV) infusions containing pegloticase 8 mg at each infusion (biweekly treatment group) or biweekly placebo infusions (placebo group). Prophylaxis against infusion-related reactions (IR) was given to all patients before each infusion: oral fexofenadine (60 mg the evening before and again before infusion); acetaminophen (1000 mg); and IV hydrocortisone (200 mg), immediately before infusion. Gout flare prophylaxis with colchicine (0.6 mg once or twice daily) or a nonsteroidal antiinflammatory drug (NSAID) was initiated 1 week before first infusion and continued throughout the study. SU was determined preceding each biweekly infusion[6] and is reported in this analysis. Plasma urate levels were also obtained and were used to define responders as per the protocol. Other outcomes were assessed at weeks 13, 19, and 25 and included response of target tophus, rated as either complete response: 100% decrease in area of the tophus; partial response: ≥ 50% decrease in tophus area; stable disease: < 50% decrease to < 25% increase in tophus area; and progressive disease: ≥ 25% increase in tophus area (as measured from digital photographs with Computer-Assisted Photographic Evaluation in Rheumatology methodology)[19]; reductions in the proportion of patients with gout flare, and in the number of flares per patient during months 1–3 and 4–6 of the trial; reductions in tender joint count (TJC) and swollen joint count (SJC); PtGA; and patient-reported changes in pain, physical function, and health-related QOL measured, respectively, by a visual analog scale (VAS), the Health Assessment Questionnaire–Disability Index Functional Index Scale (HAQ-DI FIS), the Medical Outcomes Study Short Form-36 (SF-36) physical component summary (PCS), and arthritis-specific health index (ASHI) scores. Except for pegloticase, no additional urate-lowering agents (e.g., allopurinol, febuxostat, probenecid) were administered to any group at any point during the study.

Patient groups evaluated. Four groups of patients were evaluated: (1) responders (n = 36) based on the aforementioned criteria: patients with SU < 6.0 mg/dl for ≥ 80% of the time during both months 3 and 6, the periods extending, respectively, from the Week 9 infusion to just prior to the Week 13 infusion and from the Week 21 infusion to the Week 25 final study visit; (2) modified intent to treat (mITT) nonresponders (n = 49): all nonresponders who received at least 1 infusion, including those who exited the study and were not available for the urate assessments at 3 and 6 months (some of these patients may actually have been biochemical responders to pegloticase treatment when they exited the study); (3) per-protocol (PP) nonresponders (defined for present analysis): nonresponders who received all planned pegloticase infusions in the first 3 months (n = 35) or the entire 6 months (n = 24) of the RCT, but still failed to meet the prespecified criterion of responders; and (4) patients who received placebo in the RCT (none of these met the criterion for a response to treatment).

Data analysis. Areas under the curve (AUC) of SU during the 6-month study were calculated according to the following equation:

$$AUC = \int_a^b F(X)\,dX$$

where a and b are points on the X axis and F(X) is the integral of function using SAS. Because the curves were not always continuous functions, the trapezoidal rule was used to approximate the definitive integral.

All comparisons between baseline and on-treatment values were made with Wilcoxon 2-sample test with $p < 0.05$ as the accepted level of significance.

RESULTS

Patients. The analysis included 36 responders, 49 mITT nonresponders, 39 PP nonresponders, and 43 patients who received placebo. The demographic and clinical characteristics for these patients are summarized in Table 1.

SU responses. Study results for the RCT showed, as expected, that responders had significant reductions from baseline in SU at both 3 and 6 months ($p < 0.0001$; Figure 1A). There were also significant reductions in SU for mITT (at Month 3, $p = 0.0005$) and PP (at months 3, $p = 0.001$; and 6, $p = 0.04$) nonresponders. However, these reductions in mean SU did not result in persistent SU levels < 6.0 mg/dl. No significant changes in SU were noted in the patients receiving placebo. AUC for SU (Figure 1B) indicated a sustained reduction in q2w responders that was significantly different from those for the q2w mITT and PP nonresponders and patients who received placebo for months 1–3 (all $p < 0.0001$) and months 4–6 (all $p < 0.0001$). There was also a reduction in SU in the q2w mITT and PP nonresponders that was significantly different from results for the patients who received placebo for months 1–3 (both $p < 0.0001$) and months 4–6 ($p = 0.0077$ and $p = 0.046$, respectively). It is also apparent that the SU AUC for the q2w responders was lower over the second 3 months versus the first 3-month period.

Tophus responses. Complete tophus responses occurred most frequently for responders (52.0%), but it was also noted in 25.0% of mITT nonresponders and 26.9% of PP nonresponders. In contrast, only 10% of the patients in the placebo had complete tophus responses (Figure 2). Partial responses were noted for 16% of responders, 25.0% of mITT nonresponders, 26.9% of PP nonresponders, and 20.0% of patients who received placebo. Any tophus improvement (i.e., complete or partial response) occurred in 68% of responders, 50% of mITT nonresponders, 53.8% of PP nonresponders, and only 30% of patients who received placebo.

Flares. Results for responders, mITT nonresponders, and PP nonresponders all indicated reductions in flares by Month 6 of the RCT. The decreases for the responders and mITT nonresponders achieved statistical significance ($p = 0.0009$ and $p = 0.0002$, respectively), whereas that for the PP nonresponders did not ($p = 0.0575$; Table 2). No significant changes were noted in patients receiving placebo.

TJC and SJC. Results for responders, mITT nonresponders, and PP nonresponders all indicated significant reductions in TJC (Figure 3A) and SJC (Figure 3B) by the end of the RCT ($p < 0.05$). Results for the responders also indicated signifi-

Table 1. Demographic and clinical characteristics for patients evaluated.

Characteristics	RCT Responders, n = 36	mITT RCT Nonresponders, n = 49	PP RCT Nonresponders, n = 35	Placebo, n = 43	p
Age, yrs, mean (SD)	61.2 (14.2)	52.7 (15.6)	52.6 (15.4)	55.4 (12.2)	0.02
Male sex	26 (72.2)	42 (85.7)	29 (82.9)	36 (83.7)	0.42
Disease duration, yrs, mean (SD)	17 (14.4)	14.2 (10.0)	12.3 (9.3)	13.3 (9.7)	0.61
Patients with > 1 flare in the past 18 months	33 (91.7)	44 (89.8)	31 (88.6)	37 (86.1)	0.88
Acute flares in prior 18 mos, mean (SD)	12.4 (11.6)	7.9 (9.3)	7.5 (8.4)	10.2 (16.4)	0.15
Tophus present	25 (69.4)	37 (75.5)	27 (77.1)	29 (67.4)	0.73
Serum urate, mg/dl, mean (SD)	10.1 (2.9)	9.5 (3.1)	9.3 (3.4)	9.2 (2.8)	0.41
Serum urate > 6 mg/dl	33 (91.7)	41 (85.4)	28 (80.0)	35 (83.3)	0.53
Comorbidities					
Hypertension	25 (69.4)	36 (73.5)	28 (80.0)	31 (72.1)	0.77
Dyslipidemia	21 (58.3)	21 (42.9)	16 (45.7)	19 (44.2)	0.53
Diabetes mellitus	13 (37.1)	11 (22.4)	9 (25.7)	8 (18.6)	0.32
Coronary artery disease	5 (14.3)	4 (8.2)	3 (8.6)	6 (14)	0.73
Cardiac failure	7 (20.0)	3 (3.6)	3(8.6)	6 (14)	0.30

Values are n (%) unless otherwise specified. RCT: randomized controlled trials; mITT: modified intent to treat; PP: per protocol.

cant improvements in both of these measures at 3 months post-baseline ($p < 0.05$). No significant responses were noted in patients receiving placebo.

PtGA. Results for responders, mITT nonresponders, and PP nonresponders all indicated significant improvements in PtGA at both 3 and 6 months post-baseline (all $p < 0.05$; Figure 3C). No significant changes were noted in patients receiving placebo.

Pain. Results for responders, mITT nonresponders, and PP nonresponders all indicated significant reductions in SF-36 bodily pain by the end of the RCT ($p < 0.05$; Figure 3D). All groups also had decreases in pain measured with a VAS, but only that for responders achieved statistical significance ($p < 0.05$; Figure 3E). No significant changes were noted in patients receiving placebo.

Health-related QOL. Results for the SF-36 PCS, SF-36 ASHI, and HAQ-DI FIS were variable (Table 3). Responders were the only group that showed significant improvement on the SF-36 PCS ($p = 0.02$ at 6 months), whereas nonsignificant trends in improvement were observed in the mITT and PP nonresponders, but not the placebo group. Responders, mITT nonresponders, and PP nonresponders all showed significant improvements in the SF-36 ASHI at 6 months ($p = 0.002$, $p = 0.02$, and $p = 0.005$, respectively); the PP nonresponders also showed a significant improvement from baseline at 3 months ($p = 0.03$). The PP nonresponders had a significant reduction from baseline in the HAQ-DI FIS at 6 months post-baseline ($p = 0.04$). No significant changes were noted in patients receiving placebo.

DISCUSSION

The results from these analyses indicate that despite failure to achieve the study outcome measure of urate-lowering response among the mITT and PP nonresponders in the RCT, the use of pegloticase was associated with significant improvements in a large number of clinical variables including reductions in flares, reduction of tophi, decreases in TJC and SJC, and improvements in PtGA, SF-36 pain, and SF-36 ASHI scores. It is unlikely that these improvements resulted from enrollment in a clinical trial[20], or from agents administered as prophylaxis against IR or flares, because no significant improvements were observed in the patients who received placebo, who also received prophylaxis against both IR (oral fexofenadine, acetaminophen, and intravenous hydrocortisone) and flares (colchicine or NSAID). It is also unlikely that the clinical improvements in biochemical nonresponders were related to a subset of patients who had sustained urate reductions with pegloticase, but who withdrew from the study and were thus considered nonresponders (there were 27 such patients in the 2 RCT)[6]. In this regard, results for the PP nonresponders who completed the study were similar to those for the mITT nonresponders, which included dropouts.

Biochemical nonresponders showed some clinical improvements at the end of 3 months of treatment. A possible explanation is that these patients were within a month of the time during which their SU levels were < 6 mg/dl. However, by the 3-month time frame, the mean SU levels for both groups were > 6 mg/dl and remained elevated throughout the remainder of the 6-month RCT. Notably, there were no exacerbations of clinical manifestation of gout during months 3–6 even though SU was persistently > 6.0 mg/dl during this period.

These findings are consistent with the conclusion that a transient lowering of SU might have a persistent clinical benefit, which may be of clinical relevance. There are only limited results from previous studies that have assessed the clinical effects of urate-lowering therapy in patients with gout

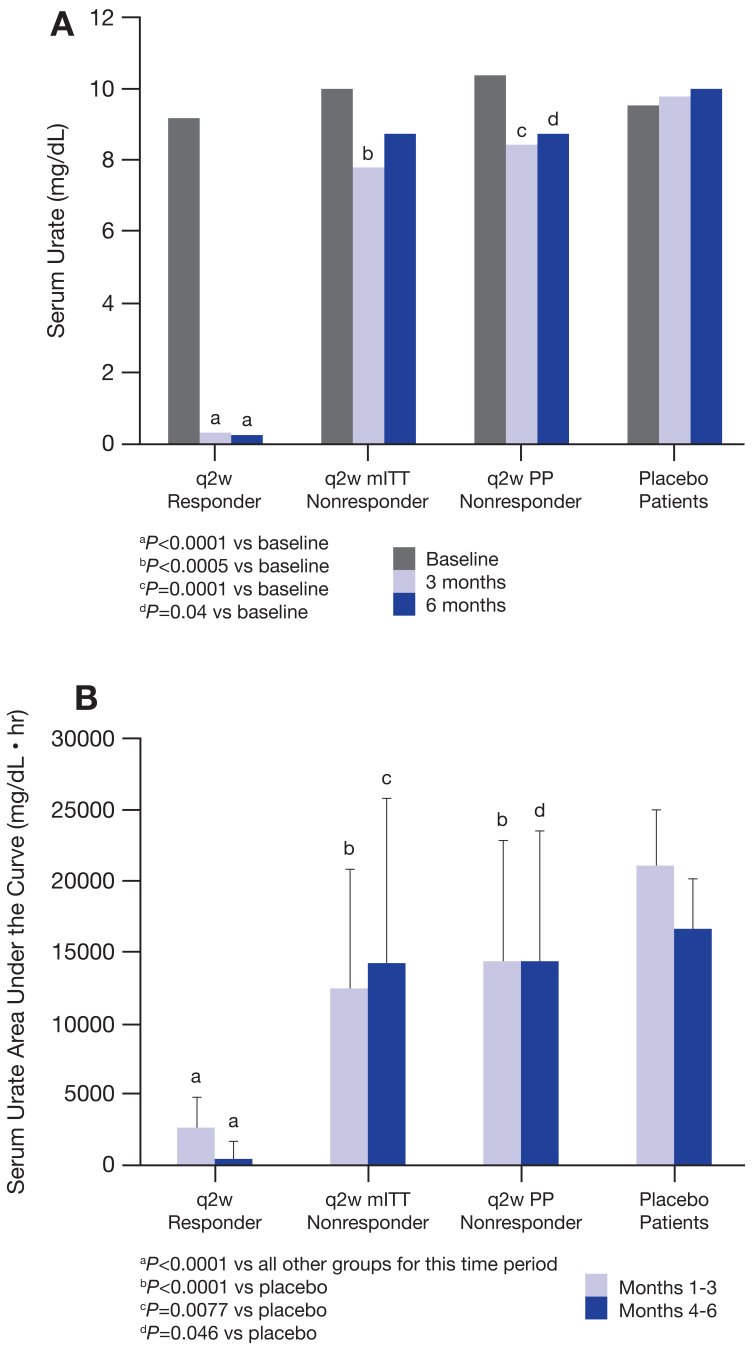

Figure 1. Serum urate (A) and serum urate AUC (B) for all study groups. mITT: modified intent to treat; PP: per protocol; q2w: every 2 weeks; AUC: area under the curve.

at early timepoints. Results from a 12-month study of patients treated with the combination of febuxostat and lesinurad indicated that the mean SU at 3 months was ~3.3 mg/dl and that there was a significant 21.1% reduction in total tophus target area at this timepoint[13]. Thus, while data are sparse, the available information is consistent with the view that 3 months of urate-lowering therapy can result in improvements in clinical outcomes. The current study shows that benefits might persist despite a subsequent rise of SU into the abnormal range. These findings raise interesting questions about the balance between extent and duration of urate lowering required to induce clinical improvement, even in persons with established gout.

The present analysis showed that improvements from baseline for multiple clinical measures continued from 3 to 6 months after the initiation of treatment in both the mITT

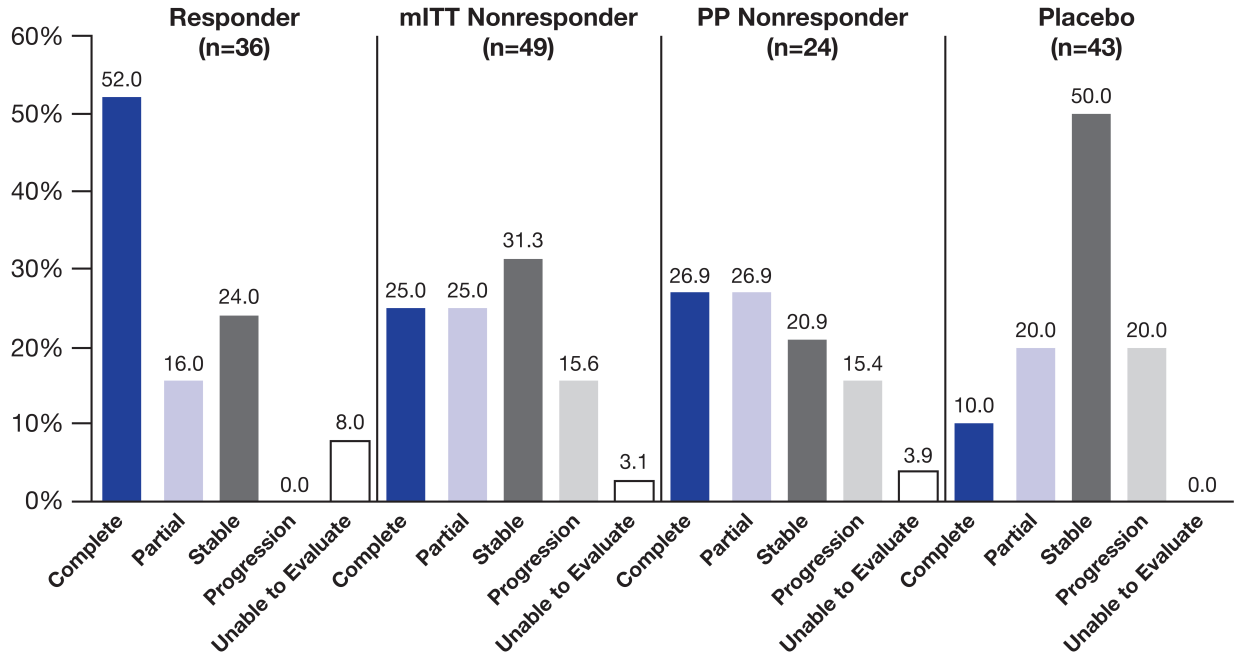

Figure 2. Tophus resolution in all study groups. mITT: modified intent to treat; PP: per protocol.

Table 2. Flares in all study groups.

Groups	Time	Mean No. Flares/ 3 Mos (SD)	p*
Responder			
n = 36	Baseline	2.1 (1.9)	–
n = 36	3 months	2.6 (2.1)	0.25
n = 36	6 months	1.0 (1.4)	0.0009
mITT nonresponder			
n = 48	Baseline	1.3 (1.5)	–
n = 49	3 months	2.1 (2.1)	0.08
n = 33	6 months	0.6 (1.0)	0.0002
PP nonresponder			
n = 24	Baseline	1.3 (1.6)	–
n = 24	3 months	1.7 (1.6)	0.4857
n = 24	6 months	0.8 (1.1)	0.0575
Placebo			
n = 43	Baseline	1.7 (2.7)	–
n = 43	3 months	1.2 (1.6)	0.12
n = 43	6 months	1.3 (1.5)	0.63

* Versus baseline. mITT: modified intent to treat; PP: per protocol.

and PP nonresponders. By 6 months of treatment, the mean SU levels in these groups had risen to > 8.0 mg/dl. In addition, results from all nonresponders in the 2 trials providing the basis for this report suggest that these levels were probably reached by weeks 6–8 of treatment[6,18]. There are at least 2 potential non-mutually exclusive explanations for the sustained clinical improvements observed in the biochemical nonresponders. First, while the SU levels in the mITT and PP nonresponders were increased at both Month 3 and Month 6, they remained significantly below pre-treatment levels, which were 9.5 mg/dl for mITT nonresponders and 9.3 mg/dl for PP nonresponders. This was reflected in the SU AUC analysis. It is reasonable to suggest that this reduction from baseline in SU supported continued improvement in clinical outcomes, even though levels remained above the proposed limit of solubility. Results from previous studies have indicated a graded relationship between urate levels and clinical outcomes for patients with gout, even when the SU remained > 6.0 mg/dl. For example, Shoji, *et al* demonstrated a significant correlation between SU and gouty attacks. This analysis indicated that a reduction in SU from 9.4 to 7.7 mg/dl resulted in a 30% reduction in attacks[14]. A second factor that may contribute to the sustained clinical responses in pegloticase biochemical nonresponders is the rapid debulking of urate crystal deposits that has been documented with this treatment[16,21,22,23,24]. It has been noted that debulking of disease and a tophus-free state can be reached within a few months of pegloticase treatment[16,24]. Even in the 2 nonresponder groups, about 50% of the patients in this study had complete or partial tophus responses. It is notable that 30% of subjects receiving placebo had a complete or partial tophus response, implying an inherent false-positive rate in this measurement of tophus resolution. Despite this, the frequency of subjects achieving a complete or partial tophus response was greater in the pegloticase nonresponders, implying a benefit for transient lowering of urate. The presence of tophi in patients with gout is associated with significantly decreased health-related QOL[25,26,27,28,29] and bodily pain measured by SF-36[26]. Results from the RCT used in this analysis showed further that patients with tophaceous gout have significantly higher numbers of tender and

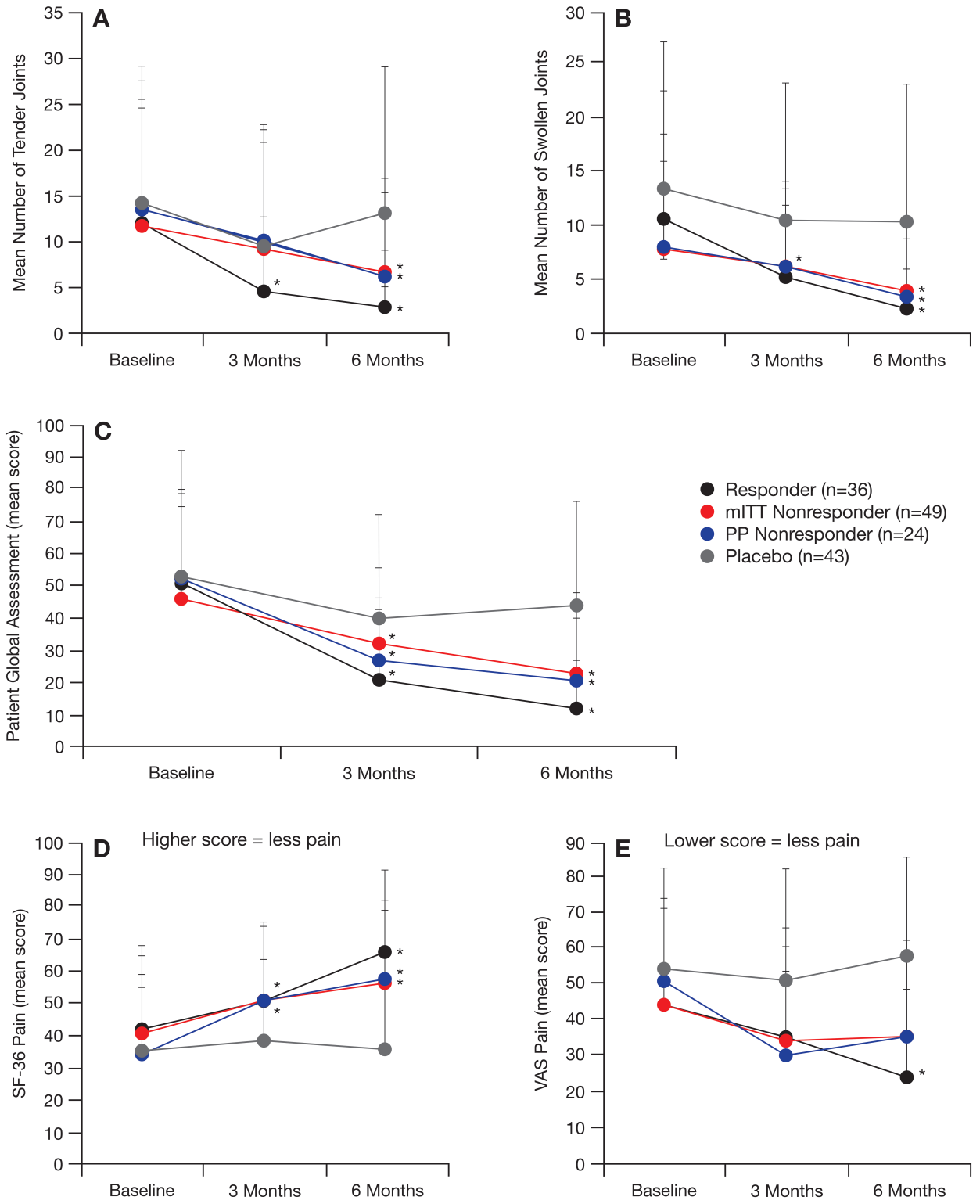

Figure 3. A and B. Tender and swollen joint counts in all study groups. C. Patient's global assessment for all study groups. D and E. SF-36 bodily pain for all study groups and VAS pain for all study groups. mITT: modified intent to treat; PP: per protocol; SF-36: Medical Outcomes Study Short Form-36 questionnaire; VAS: visual analog scale.

Table 3. Measures of physical function, arthritis-specific health index, and disability in all study groups.

Groups	Time	SF-36 PCS		SF-36 ASHI		HAQ-DI FIS	
		Mean (SD)	p*	Mean (SD)	p*	Mean (SD)	p*
Responder							
n = 36	Baseline	35.1 (10.7)	–	55.4 (29.1)	–	1.0 (0.8)	–
n = 36	3 mos	38.6 (12.3)	0.24	65.9 (31.4)	0.18	0.9 (0.9)	0.40
n = 36	6 mos	41.6 (11.2)	0.02	78.8 (28.3)	0.002	0.8 (0.8)	0.20
mITT Nonresponder							
n = 47	Baseline	35.2 (11.1)	–	53.6 (28.3)	–	1.2 (0.9)	–
n = 49	3 mos	36.7 (10.0)	0.45	62.8 (24.9)	0.11	1.1 (0.8)	0.46
n = 49	6 mos	39.2 (11.5)	0.15	69.7 (29.1)	0.02	0.9 (0.8)	0.20
PP Nonresponder							
n = 22	Baseline	33.8 (10.8)	–	47.4 (26.9)	–	1.4 (0.9)	–
n = 24	3 mos	37.0 (10.2)	0.20	65.0 (23.1)	0.03	1.0 (0.8)	0.17
n = 22	6 mos	39.4 (10.1)	0.07	70.3 (24.6)	0.005	0.9 (0.7)	0.04
Placebo							
n = 43	Baseline	31.0 (11.1)	–	45.8 (27.3)	–	1.2 (1.0)	–
n = 42	3 mos	32.4 (11.9)	0.66	49.5 (30.2)	0.78	1.3 (1.0)	0.8
n = 38	6 mos	30.2 (11.9)	0.78	46.6 (29.0)	1.0	1.3 (0.9)	0.7

* Versus baseline. ASHI: arthritis-specific health index score; HAQ-DI FIS: Health Assessment Questionnaire–Disability Index Functional Index Scale; mITT: modified intent to treat; PCS: physical component summary score; PP: per protocol; SF-36: Medical Outcomes Study Short Form-36 questionnaire.

swollen joints, significantly worse PtGA scores and HAQ-DI functionality scores, and significantly lower SF-36 ASHI scores versus patients without tophi[30]. Thus, it is reasonable to suggest that a profound transient reduction in SU and the associated debulking of urate crystal deposits may have contributed to the sustained clinical benefit of pegloticase in biochemical nonresponders. The suggestion that an increase in SU after it has been decreased to below the target of < 6 mg/dl need not result in a rapid return of signs and symptoms is supported by results of a previous study that evaluated the effects of treatment withdrawal in patients who had responded biochemically to urate-lowering therapy. The mean time to clinical relapse (defined by gouty symptoms and appearance of tophi) for patients whose SU increased to ≥ 8.75 mg/dl after treatment cessation was 34 months[31].

The results of this analysis indicate that chronic refractory gout patients not achieving a protocol-defined biochemical response may still have significant clinical benefits with pegloticase treatment. This suggests that the substantial, although transient, reduction in SU achieved in patients categorized as nonresponders in the RCT can result in sustained clinical benefit. In such patients, examination of a strategy of returning to oral management (e.g., allopurinol, febuxostat) after initial pegloticase treatment deserves formal examination.

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