Editorial

Debulking the Urate Load to Feel Better

Contrary to the general assumption that gout is a benign condition, epidemiologic studies have demonstrated gout to be associated with increased risk of cardiovascular events and all causes of mortality[1]. From a social viewpoint, gout also has a substantial effect on work, resulting in work absence and decreased productivity[2]. Moreover, in some patients, it can lead to severely impaired quality of life. For example, scores of the Medical Outcomes Survey Short-Form 36 (SF-36) for patients with gout were found comparable to those of patients with severe, debilitating rheumatoid arthritis[3]. Also, Becker, *et al* found that subjects with treatment-failure gout had mean SF-36 scores that were analogous to those of healthy individuals aged 75 years and older[4].

Progression of gout from solely acute flares to severe chronic disease, characterized by palpable tophi combined with urate crystal arthropathy, is most often the result of failure of urate-lowering therapy (ULT) to reach the target of 6 mg/dl to achieve crystal dissolution, and/or poor adherence of patients to ULT[5]. This failure to lower serum uric acid (sUA) levels below the European recommended cutoff of 6 mg/dl (360 μM)[6] or the British recommended cutoff of 5 mg/dl (300 μM)[7] usually occurs in patients intolerant to, or whose disease is refractory to, currently available ULT agents. This is the case with allopurinol in particular because of the frequency of allergic reactions or when medical comorbidities, mainly renal failure, limit the extent of its use. In organ transplant recipients, for whom therapy to prevent graft rejection includes azathioprine, use of xanthine oxidase inhibitors such as febuxostat is contraindicated, which explains the frequent failure to lower sUA levels in such patients. Thus, despite the availability of ULT, a subset of patients have refractory gout that manifests as recurrent gout flares, chronic arthritis, and progressive urate crystal deposition[8].

For these difficult-to-treat patients, about 3% of the gouty population in the United States, pegloticase is an attractive alternative therapeutic. Pegloticase is a recombinant porcine uricase produced in *Escherichia coli* and a tetrameric enzyme. Each subunit is conjugated with several strands of a 10-kDa monomethoxypoly(ethylene glycol) (mPEG). The rationale for the addition of mPEG to the regimen is to reduce the potential for immunogenicity and to increase circulation half-life as compared with the non-PEGylated uricases[9,10].

The efficacy of pegloticase to efficiently lower sUA in patients with chronic gout refractory to conventional therapy was demonstrated in two 6-month, randomized, placebo-controlled, phase-3 replication study trials[11]. A total of 225 participants were randomized to receive pegloticase (8 mg by intravenous infusion every 2 or 4 weeks) or placebo in a 2:2:1 ratio; 212 subjects received at least 1 infusion of study treatment, and 157 patients completed the protocol treatment. Pegloticase was found to be a rapid and potent ULT, decreasing sUA to < 6 mg/dl within 24 h after the first infusion in all treated patients. The proportion of patients achieving the primary endpoint — sUA level < 6 mg/dl for more than 80% of the time during Months 3 and 6 — was 42% and 35% for patients receiving 8 mg pegloticase every 2 and 4 weeks, respectively, compared with 0% for the placebo group. Moreover, pegloticase treatment was associated with greater resolution of at least one tophus: 40% and 21% with 8 mg pegloticase every 2 and 4 weeks, respectively, compared with 7% for the placebo group. Unexpectedly, pegloticase was shown to be immunogenic in some patients, and the presence of antibodies, mainly directed against the methoxy group of the PEG[12], was associated with a decrease in urate-lowering effects and a higher rate of infusion reactions[11].

In this issue of *The Journal*, Strand, *et al* extend the previous results of these phase-3 studies by presenting the efficacy of pegloticase for patient-reported outcomes (PRO)[13], in particular the Medical Outcomes Study Short Form-36 (SF-36), which assesses health-related quality of life (HRQOL) in 9 domains, and the Health Assessment Questionnaire Disability Index (HAQ-DI), which assesses disease-related physical function.

The first important results from this study are from the

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baseline values of the PRO, which underline the severity of refractory gout: mean HAQ-DI scores for placebo and treatment groups were comparable to those reported for patients with active rheumatoid arthritis[14]. In addition, the baseline SF-36 scores for these groups were lower than age- or gender-matched US normative values, and lower than scores for an osteoarthritis population, which reflects the major influence of gout on HRQOL.

At Week 25, patients receiving pegloticase every 2 or 4 weeks achieved significant improvements in function and pain as determined by the SF-36 physical component summary (PCS), HAQ-DI, pain assessment, and patient global assessment relative to subjects receiving placebo. The proportion of subjects reporting an improvement greater than the minimum clinically important difference (MCID) for the HAQ-DI was 45% and 48% for groups receiving 8 mg pegloticase every 2 and 4 weeks, respectively, compared with 16% for the placebo group ($p < 0.001$).

This proportion for the SF-36 PCS in the 2 treatment groups was 64% and 61%, respectively, and 29% for the placebo group ($p < 0.01$). The study arms did not differ in change from baseline to Week 25 in SF-36 mental component summary scores.

Given the effects of severe gout on patient HRQOL and functioning, these results are noteworthy because they show that pegloticase can improve PRO. Assessment of these patient-centered outcomes is of major interest in clinical trials of refractory gout. Indeed, sUA level, used as the primary endpoint for investigating several new ULT such as febuxostat and lesinurad[15], is not a clinical severity marker and is not related to any HRQOL or disability measure[4]. Moreover, in subjects with severe tophaceous gout, sUA levels represent a small fraction of total body urate stores, compared with healthy individuals, in whom about 25% of the total body urate is circulating in plasma.

However, assessment of PRO is challenging in gout mainly for 2 reasons[16]: First, poor HRQOL and functional limitation in severe gout can be due in part to frequent comorbidities, especially cardiovascular as seen in the pegloticase phase-3 trials[11], rather than the gout itself[17]. The second issue is related to the natural course of gout, which implies assessing acute flares and chronic gout separately.

In recent years, the OMERACT (Outcome Measures in Rheumatology) gout group[17,18] and others[19,20] have expended considerable effort to assess the metrologic properties of several outcome measures that can be used for chronic gout. The following outcomes endorsed by the OMERACT group are pain [visual analog scale (VAS)], patient global assessment (VAS), the HAQ-DI, and the SF-36[17,18]. Nevertheless, statistically significant improvement in these PRO at the group level does not imply that these differences are meaningful to individuals. Therefore, the use of the minimum clinically important difference (MCID) — the smallest difference in a score that is considered to be worthwhile or important — as in the study by Strand and colleagues[13], gives an idea of the proportion of patients who feel better. For practical relevance, the proportion of patients receiving pegloticase who reached the Patient Acceptable Symptom State — a state in which patients consider their condition satisfactory or acceptable, and often interpreted as feeling good — would also have been of interest.

Lastly, these interesting data also implicitly raise several questions: Once patients treated with pegloticase feel better — or even better, feel good[21] — and the sUA levels are maintained at below 6 mg/dl, what should we do? Should we continue the pegloticase treatment with the same regimen or with less-frequent infusions? Or should we consider the pegloticase as a bridge therapy and therefore switch to an oral ULT? Further studies are required to determine the best therapeutic strategy to maintain a state of well-being for our gouty patients once their tophi have been debulked.

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