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Reducing Immunogenicity of Pegloticase With Concomitant Use of Mycophenolate Mofetil in Patients With Refractory Gout: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial

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Objective. Pegloticase is used for the treatment of severe gout, but its use is limited by immunogenicity. This study was undertaken to evaluate whether mycophenolate mofetil (MMF) prolongs the efficacy of pegloticase.

Methods. Participants were randomized 3:1 to receive 1,000 mg MMF twice daily or placebo for 14 weeks, starting 2 weeks before receiving pegloticase and continuing while receiving intravenous pegloticase 8 mg biweekly for 12 weeks. Participants then received pegloticase alone from week 12 to week 24. The primary end points were the proportion of patients who sustained a serum urate level of ≤6 mg/dl at 12 weeks and the rate of adverse events (AEs). Secondary end points included 24-week durability of serum urate level ≤6 mg/dl. Fisher's exact test and Wilcoxon's 2-sample test were used for analyses, along with Kaplan-Meier estimates and log rank tests.

Results. A total of 32 participants received ≥1 dose of pegloticase. Participants were predominantly men (88%), with a mean age of 55.2 years, mean gout duration of 13.4 years, and mean baseline serum urate level of 9.2 mg/dl. At 12 weeks, a serum urate level of ≤6 mg/dl was achieved in 19 (86%) of 22 participants in the MMF arm compared to 4 (40%) of 10 in the placebo arm ($P = 0.01$). At week 24, the serum urate level was ≤6 mg/dl in 68% of MMF-treated patients versus 30% of placebo-treated patients ($P = 0.06$), and rates of AEs were similar between groups, with more infusion reactions occurring in the placebo arm (30% versus 0%).

Conclusion. Our findings indicate that MMF therapy with pegloticase is well tolerated and shows a clinically meaningful improvement in targeted serum urate level of ≤6 mg/dl at 12 and 24 weeks. This study suggests an innovative approach to pegloticase therapy in gout.

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INTRODUCTION

Gout is a common chronic inflammatory arthritis associated with acute flares that when left untreated results in chronic and potentially destructive arthritis and tophi formation. Pegloticase is a recombinant, PEGylated uricase, approved in the US for the treatment of patients with gout who fail to respond to conventional oral urate-lowering therapy (1). Despite its remarkable efficacy as "debulking therapy" in people with severe gout (2), its potent immunogenic response leads to clearing antidrug antibodies and higher rates of infusion reaction and limits clinical response (3,4). A relationship between the loss of urate-lowering efficacy of pegloticase, indicated by an increase in serum urate levels, and high-titer antibody formation was noted in post hoc analyses in 2 pivotal studies (1,5). Participants with high anti-pegloticase antibody titers experienced a significant loss of pegloticase activity, which is attributed to faster drug clearance in the presence of these antibodies. Sixty-nine (41%) of 169 patients receiving pegloticase developed high-titer anti-pegloticase antibodies and subsequently lost response to the drug (6). In addition, 60% of participants with high titers developed an infusion reaction (1,7).

Based in part on the ability of immunomodulatory drugs such as methotrexate (MTX) to attenuate antidrug antibodies when using certain biologics, the co-administration of such agents could disrupt the ability of pegloticase to induce production of anti-pegloticase antibodies, thus mitigating the loss of efficacy (6–9). Indeed, recently published case series suggest that MTX, azathioprine, and leflunomide may attenuate pegloticase-induced antidrug antibody formation (10–13). Through inhibition of T and B cell proliferation (14,15), mycophenolate mofetil (MMF) is another immunomodulating drug commonly and successfully used in other rheumatic diseases, with an established safety profile in patients with chronic kidney disease, which is a frequent comorbidity among patients with uncontrolled gout (16–19). We tested the feasibility of using a short-term course of MMF, started prior to the initiation of pegloticase and continued though the first 12 weeks of combined therapy, to increase the proportion of patients who were able to achieve a sustained reduction in serum urate level during the course of pegloticase therapy, thus improving the efficacy and safety of pegloticase infusions.

PATIENTS AND METHODS

Study design. We designed a phase II, proof-of-concept, randomized, placebo-controlled trial of short-term MMF versus placebo. Participants from 5 large practices were randomized in a 3:1 ratio by site to receive either MMF or placebo initiated 2 weeks before the administration of pegloticase. Pegloticase was administered at the US Food and Drug Administration (FDA)–approved dose of 8 mg intravenously (IV) every 2 weeks for a total of 12 infusions. Based on an informal survey of 15 rheumatologists who preferred MMF or MTX over other drugs, we chose MMF to serve as a potential immunomodulator to pegloticase in a phase II, proof-of-concept trial. MMF or placebo was continued for the first 12 weeks of the 24-week duration of pegloticase therapy. All participants then received pegloticase alone for the remaining 12 weeks. The rationale for choosing 12 weeks as the primary end point was: 1) historical cohort data demonstrating the development of antibodies in the first 6 weeks of pegloticase use (11), 2) concerns about the possible safety of concomitant use of MMF with pegloticase for a longer duration, and 3) interest in determining if the durability of response changed when MMF treatment was stopped after 12 weeks.

The trial was approved by the Institutional Review Board (IRB) at each participating research center, and each patient signed the IRB-approved consent form. We received the Investigational New Drug approval from the FDA on November 29, 2017, and the study was registered at ClinicalTrials.gov (identifier: NCT03303989) on September 29, 2017. The study inclusion criteria were: 1) age >18 years, 2) fulfillment of the 2015 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria for gout (20), 3) presence of chronic refractory gout, defined as signs and symptoms inadequately controlled with urate-lowering therapy (e.g., xanthine oxidase inhibitors or uricosuric agents) at a medically appropriate dose or contraindication to these drugs, 4) hyperuricemia (i.e., serum urate level >6 mg/dl) at the screening visit, and 5) no previous treatment with pegloticase or other uricase therapies. Exclusion criteria were weight >160 kg (352.74 lb), infection in the prior 2 weeks, and an immunocompromised status.

Study visits and drug administration. Study visits included a screening visit to confirm study eligibility, explain procedures, and allow participants to engage in the informed consent process. Following the screening visit, participants were randomized and began a run-in period during which they received placebo or MMF at 500 mg twice per day for 7 days. If tolerated, the dose was titrated up to 1,000 mg twice per day for an additional 7 days prior to the initial pegloticase infusion. Participants who were not able to tolerate the placebo or MMF dose due to gastrointestinal or other adverse events (AEs) during the run-in period were withdrawn from the study and not followed up further. All participants received gout flare prophylaxis (colchicine 0.6 mg/day or low-dose nonsteroidal antiinflammatory medication) starting 7 days prior to the first pegloticase infusion. For each of the pegloticase infusions, consistent with standard of care for pegloticase administration, all participants received pre-infusion prophylaxis (i.e., oral fexofenadine [60 mg] the night before, oral fexofenadine [60 mg] and acetaminophen [1,000 mg] the morning of the infusion, and IV hydrocortisone [200 mg] immediately prior to the infusion). If an infusion reaction occurred or there were 2 consecutive measurements of serum urate level >6 mg/dl prior to the pegloticase infusion,

pegloticase infusions were discontinued. The participant was considered a nonresponder and was followed up for all study visits as scheduled.

It was expected that many participants would continue to have gout flares during the study, since gout flares typically occur early in the course of pegloticase treatment (21). Colchicine 0.6 mg up to a maximum of 3 times per day (22,23) for 1 week was the preferred therapy to manage acute flares, at the discretion of the managing physician/investigator. An alternative or additional treatment was a 7-day course of glucocorticoids or the use of nonsteroidal antiinflammatory drugs. Adequate pain control was maintained by the study physicians, who also served as the managing physicians for all gout care for study participants.

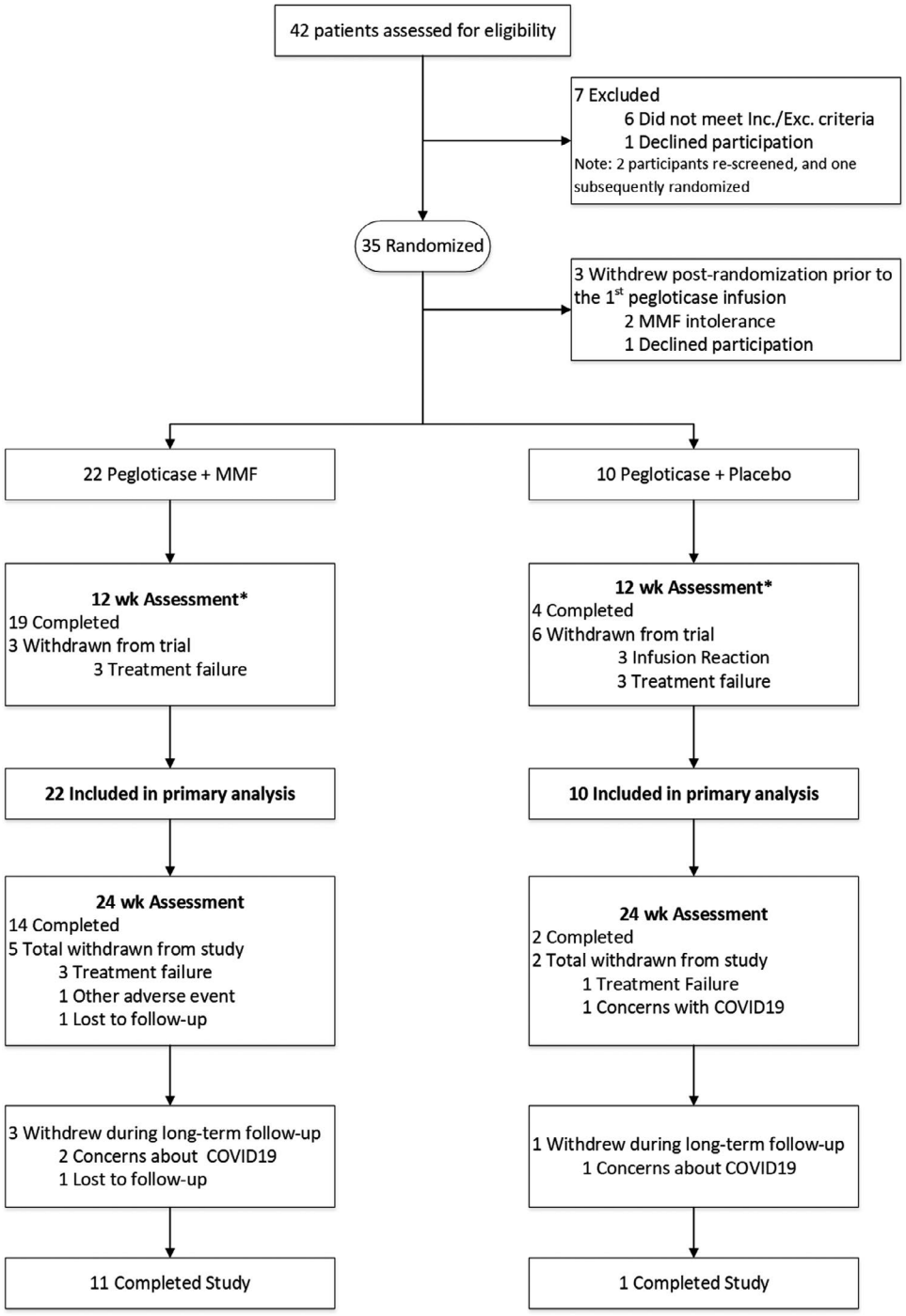

Figure 1. Flow diagram showing the distribution of the study subjects. Details are given according to the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting randomized controlled trials. Asterisk indicates the primary end point (12 weeks). Inc/Exc = inclusion/exclusion; MMF = mycophenolate mofetil.

Outcome measures. The primary clinical end points were 1) the proportion of participants in whom a serum urate level of ≤6 mg/dl was achieved and maintained over 12 weeks in the MMF + pegloticase group versus the placebo + pegloticase group, and 2) the incidence and types of AEs/infusion reactions during the study. The secondary clinical end points were 1) 6-month durability of immunomodulation after discontinuation of the short course of MMF according to a) the absolute change in serum urate level from baseline to week 24, and from week 12 to week 24, and b) the proportion of participants with serum urate levels ≤6 mg/dl through 24 weeks, and from week 12 to week 24; and 2) patient-reported outcomes using the National Institutes of Health–supported Patient-Reported Outcomes Measurement Information System (PROMIS) (24,25) and Gout Impact Scale (GIS) (26,27) instruments. AEs were collected and summarized based on severity and organ systems.

Randomization. Participants were randomized in a 3:1 ratio to receive either MMF + pegloticase or placebo + pegloticase. Randomization allocation was balanced over time and by site using a double-blind design. Treatment assignment was determined by a random number generator and stratified by site using a central randomization system to ensure proper allocation. Subjects who dropped out during the run-in period (before they received pegloticase) would not provide scientifically meaningful data and were not counted in the required sample size, and thus they were replaced.

Data analyses. Descriptive analyses (the mean ± SD, median [interquartile range (IQR)], and frequency distributions [%]) were conducted to describe the study subjects. Fisher's exact tests and Wilcoxon's 2-sample tests were performed to compare baseline and clinical characteristics between treatment groups as appropriate. The efficacy of MMF was assessed as the proportion of responders in the MMF + pegloticase group compared to the placebo + pegloticase group. Rates of the primary outcome were compared using proportions and 95% confidence intervals and tested for differences using Fisher's exact test. To quantify the efficacy of MMF, Kaplan-Meier estimates and a log rank test were performed to compare survival curves between groups. AEs across groups were summarized as frequencies and percentages. Continuous secondary outcome variables were summarized as the mean ± SD, and/or median (IQR) with 95% confidence intervals and compared by groups using *t*-tests or Wilcoxon's tests as appropriate. All hypothesis tests were 2-tailed, and *P* values less than 0.05 were considered significant. Analyses were conducted using SAS, version 9.4.

Sample size. The study was designed assuming a historical responder status (i.e., success rate) for pegloticase of 40% (6). The goal of this proof-of-concept study was to reduce the expected 60% failure rate by at least half. Therefore, we hypothesized that MMF + pegloticase would yield a success rate of at least 70% (at week 12). A decision matrix based on the differences in failures between MMF + pegloticase and placebo + pegloticase was constructed using Fisher's exact test. This decision matrix to pursue a subsequent study represented the area that achieves a significant (2 tailed $P < 0.10$) Fisher's exact test that MMF + pegloticase is better than placebo + pegloticase. In this proof-of-principle study, we calculated that we needed to have a minimum of 20 informative participants receiving MMF + pegloticase therapy (i.e., participants who achieve either pegloticase responder or nonresponder status [our primary end point]).

RESULTS

Baseline characteristics of the participants. Five sites in the US screened 42 participants with uncontrolled gout based on the inclusion and exclusion criteria between May 2018 and October 2019. Figure 1 (Consolidated Standards of Reporting Trials [CONSORT] diagram) provides details on the 35 participants who were randomized. Three participants withdrew after randomization but prior to the first pegloticase infusion and were not counted in the required sample size; 32 participants received ≥1 dose of pegloticase and were included in modified intent-to-treat analyses. The baseline characteristics of the 32 participants (22 in the MMF + pegloticase group and 10 in the placebo + pegloticase group), including gout flares, severity of disease, and oral urate-lowering therapy, were similar across the 2 treatment arms (Table 1). At screening, the majority of participants were receiving optimized urate-lowering therapy (59% were receiving allopurinol and 16% were receiving febuxostat); 63% of the participants reported >1 flare in the past year.

Participants at baseline were predominantly men (88%) and White (78%) and had a mean ± SD age of 55.2 ± 9.7 years. The mean ± SD duration of gout was 13.4 ± 9.0 years, and the mean ± SD serum urate level was 9.2 ± 1.6 mg/dl. Tophi were present in 88% of the participants, and the mean ± SD ACR/EULAR gout criteria score was 13.7 ± 2.8, indicating a high burden of gout. At baseline the MMF arm and placebo arms had similar comorbidities, including hypertension (82% versus 70%), diabetes mellitus/metabolic syndrome (14% versus 20%), coronary artery disease/peripheral vascular disease (36% versus 60%), body mass index >30 (86% versus 90%), and renal insufficiency (defined as an estimated glomerular filtration rate [eGFR] of <90 ml/minute; 73% versus 70%).

Primary outcomes. At week 12, the primary outcome (serum urate level ≤6 mg/dl) was achieved in 19 (86%) of 22 participants in the MMF + pegloticase arm compared to 4 (40%) of 10 participants in the placebo + pegloticase arm ($P = 0.01$). Figure 2 demonstrates that the proportion of subjects maintaining a serum urate level of <6 mg/dl at 12 weeks was significantly greater in the MMF + pegloticase arm ($P = 0.02$). In our post hoc analysis, we examined a different

Table 1. Baseline demographic and clinical characteristics of the patients with gout treated with MMF and pegloticase or with placebo and pegloticase*

Characteristic	MMF + pegloticase (n = 22)	Placebo + pegloticase (n = 10)
Sex, no. (%) male	19 (86)	9 (90)
Age, years	55.0 ± 9.4	55.5 ± 10.7
2015 ACR/EULAR criteria points	13.5 ± 2.8	13.8 ± 2.7
Gout flare history		
Flare within last year, no. (%)	15 (68)	5 (50)
Number of flares in the last year, median (IQR)	1 (0–2)	1 (0–1)
Age at diagnosis, years	40.9 ± 14.7	42.1 ± 12.6
Duration of gout, years	13.3 ± 9.8	13.4 ± 7.4
PROMIS items		
Pain intensity T score†	50.8 ± 11.3	45.0 ± 12.4
Physical function T score‡	37.5 ± 7.8	33.8 ± 6.4
Pain score§	4.5 ± 4.0	2.8 ± 3.3
Gout impact score¶	45.7 ± 7.5	46.4 ± 7.1
Oral urate-lowering medications, no. (%)		
Allopurinol	13 (59)	6 (60)
Febuxostat	4 (18)	1 (10)
Acute gout therapy, no. (%)		
Colchicine	9 (41)	5 (50)
NSAIDs	16 (73)	5 (50)
Corticosteroids	4 (18)	2 (20)
No. of alcoholic drinks/day, no. (%)		
0	11 (50)	3 (30)
1–2	7 (32)	4 (40)
>2	4 (18)	3 (30)
Serum urate level, mg/dl	8.9 ± 1.8	9.8 ± 1.3
Serum urate level, no. (%)		
≤6 mg/dl	2 (9)	0 (0)
>6 mg/dl	20 (91)	10 (100)
CKD eGFR, mean ± SD#	81.3 ± 29.3	78.2 ± 18.4
45–59 ml/minute/1.73 m^2, no. (%)	4 (18)	2 (20)
ml/minute/1.73 m^2, no. (%)	12 (55)	5 (50)
>90 ml/minute/1.73 m^2, no. (%)	6 (27)	3 (30)
Presence of tophi, no. (%)	19 (86)	9 (90)
BMI, no. (%)		
25 to <30	3 (14)	1 (10)
30 to <45	18 (82)	7 (70)
≥45	1 (4)	2 (20)
Comorbidity, no. (%)		
Diabetes mellitus/metabolic syndrome	3 (14)	2 (20)
CVA/PVD/heart disease	8 (36)	6 (60)
Systemic hypertension	18 (82)	7 (70)
Dyslipidemia	8 (36)	4 (40)
Kidney stones	4 (18)	5 (50)

* Except where indicated otherwise, values are the mean ± SD. MMF = mycophenolate mofetil; ACR = American College of Rheumatology; EULAR = European Alliance of Associations for Rheumatology; IQR = interquartile range; PROMIS = Patient-Reported Outcomes Measurement Information System; NSAIDs = nonsteroidal antiinflammatory drugs; eGFR = estimated glomerular filtration rate; BMI = body mass index; CVA = cerebrovascular accident; PVD = peripheral vascular disease.
† Higher scores indicate more pain intensity.
‡ Lower scores indicate more physical limitations.
§ Range 0–10, with 10 indicating worst imaginable pain.
¶ Range 0–96, with higher scores indicating greater severity.
# Determined by the Chronic Kidney Disease Epidemiology Collaboration formula.

cut point for serum urate level of <5 mg/dl. Using this cutoff, there was a significant difference between treatment arms in the primary end point at week 12 (86% in the MMF + pegloticase group versus 30% in the placebo + pegloticase group; $P < 0.05$).

A total of 54 AEs were reported by 22 participants during the study period, with estimated rates of AEs generally similar between groups, not accounting for exposure time (Table 2). The most commonly reported AEs were musculoskeletal (41% in

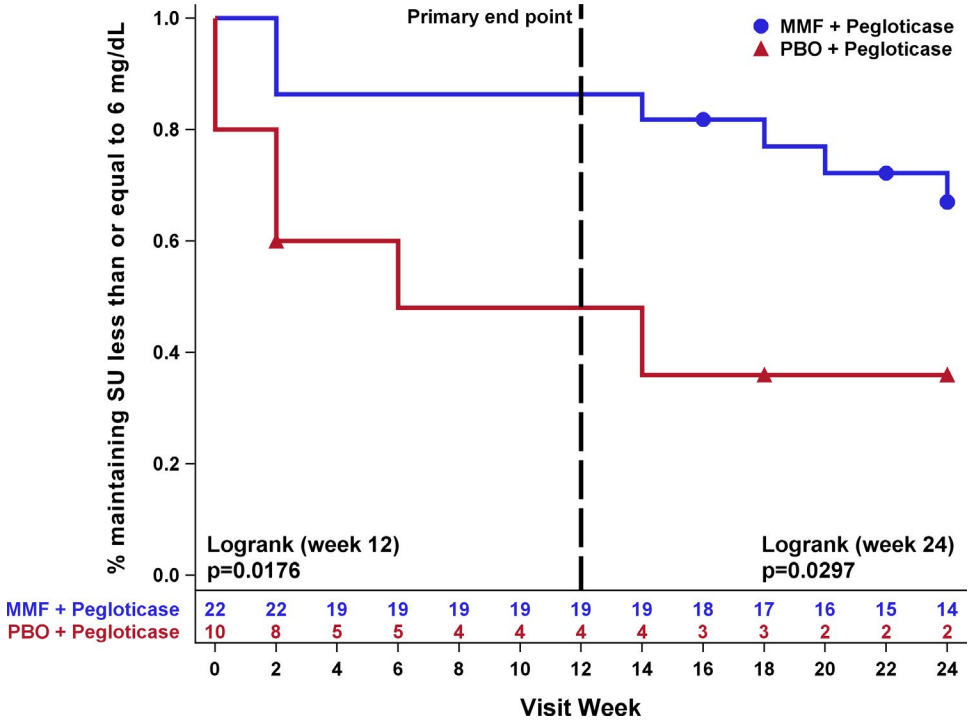

Figure 2. Kaplan-Meier estimates of the proportion of patients with gout treated with mycophenolate mofetil (MMF) and pegloticase or placebo (PBO) and pegloticase who maintained a serum urate (SU) level of ≤6 mg/dl over the 24-week study period. One participant in the placebo + pegloticase group was censored at week 18; therefore, the number of participants in this group was 2 from week 20 to week 24. However, the probability of "surviving" an interval did not change at a censored time; rather, it changed at a failure time. The dashed line indicates the beginning of treatment with pegloticase only.

the MMF group versus 10% in the placebo group) which included arthralgia, myalgia, low back pain, orthopedic trauma, bursitis tendonitis, and muscle cramps (not accounting for exposure time). Following musculoskeletal disorders, the most common AEs in the MMF + pegloticase group were gastrointestinal disorders (18% versus 10% in the placebo group), respiratory issues (18% versus 0%), infections (9% versus 0%), and other (e.g., abnormal blood tests, anxiety, and fatigue; 41% versus 50%). Four patients (3 in the MMF + pegloticase group) were found to have a transient elevation in transaminase levels, and 1 patient in the placebo + pegloticase group had a reversible decline in hemoglobin and hematocrit levels. Rates of AEs per month were similar between groups: 0.3 in the MMF + pegloticase group and 0.4 in the placebo + pegloticase group. Infusion reactions occurred in 3 participants in the placebo arm (30%) compared to none in the MMF + pegloticase arm. Two participants experienced infusion reactions during their first infusion, and the third participant had an infusion reaction during the second infusion. One infusion reaction was classified as serious and involved hospitalization. All infusion reactions resolved, and no deaths occurred.

A total of 4 serious AEs (SAEs) occurred in 3 participants during the study period. These included the 1 serious infusion reaction in the placebo + pegloticase arm, and 3 SAEs in the MMF + pegloticase arm that were unrelated to the study drug (e.g., motor vehicle crash) or possibly related to the study drug (e.g., chest pain and abdominal pain). All SAEs resolved, and no deaths or other unanticipated problems were reported in either arm.

Table 2. Treatment-related AEs in patients with gout treated with MMF and pegloticase or with placebo and pegloticase*

Adverse event	MMF + pegloticase (n = 22)	Placebo + pegloticase (n = 10)
Any AE, no. (%)	15 (68)	7 (70)
Any SAE, no. (%)†	2 (9)	1 (10)
Discontinuation from treatment due to AE, no. (%)	1 (5)	3 (30)
Most commonly reported AEs, no. (%) of patients [total number of events]		
Cardiac	2 (9) [2]	1 (10) [1]
Gastrointestinal	4 (18) [4]	1 (10) [1]
Infections	2 (9) [2]	0 (0) [0]
Musculoskeletal‡	9 (41) [19]	1 (10) [2]
Respiratory	4 (18) [4]	0 (0) [0]
Skin	2 (9) [2]	1 (10) [1]
Other	9 (41) [11]	5 (50) [5]

* Adverse events (AEs) are reported by category only. AEs that occurred in >5% of patients (across both study arms) are included. MMF = mycophenolate mofetil.
† Serious AEs (SAEs) included infusion reaction, motor vehicle crash, chest pain, and abdominal pain.
‡ Includes arthralgia, myalgia, low back pain, orthopedic trauma, bursitis tendonitis, and muscle cramps.

Table 3. Primary efficacy outcome and secondary clinical outcomes*

	MMF + pegloticase, % (95% CI) (no.) (n = 22)	Placebo + pegloticase, % (95% CI) (no.) (n = 10)	Difference between groups, % (95% CI)	MMF + pegloticase, median (IQR)/ mean ± SD (no.)	Placebo + pegloticase, median (IQR)/ mean ± SD (no.)	Mean difference (95% CI)
Primary outcome†						
Serum urate ≤6 mg/dl up to week 12	86 (65, 97) (19)	40 (12, 74) (4)	46 (13, 80)	–	–	–
Secondary outcomes				–	–	–
Serum urate ≤6 mg/dl up to week 24	68 (49, 88) (15)	30 (2, 58) (3)	38 (4, 73)	–	–	–
Serum urate ≤6 mg/dl from week 12 to week 24	79 (54, 94) (15)‡	75 (19, 99) (3)§	4 (−42, 50)	–	–	–
Absolute serum urate change up to week 24	–	–	–	7.5 (1.8–8.9)/ 5.7 ± 4.0 (22)	3.1 (1.4, 5.7)/ 4.2 ± 4.1 (9)	1.5 (−1.8, 4.7)
Absolute serum urate change from week 12 to week 24	–	–	–	0.1 (0, 5.2)/ 1.9 ± 3.0 (19)	0.05 (0, 0.2)/ 0.1 ± 0.1 (4)	1.8 (−1.3, 5.0)
PROMIS pain intensity T score at 12 weeks¶	–	–	–	49.4 (43.5, 57.5)/ 48.8 ± 9.2 (19)	49.4 (20.2, 52.1)/ 47.2 ± 6.2 (3)	1.5 (−10.1, 13.1)
PROMIS physical function T score¶	–	–	–	34.4 (29.1, 45.3)/ 37.2 ± 11.0 (19)	32.1 (29.1, 1.8)/ 34.3 ± 6.6 (3)	2.8 (−11.0, 16.7)
Pain score#	–	–	–	5.5 (3.0, 8.0)/ 5.4 ± 3.0 (10)	4.5 (3.5, 7.5)/ 5.5 ± 3.1 (4)	−0.1 (−4.0, 3.8)
Revised gout impact score at 12 weeks**	–	–	–	44.0 (39.0, 49.0)/ 43.7 ± 6.9 (19)	38.0 (37.0, 47.0)/ 40.7 ± 5.5 (3)	3.0 (−5.8, 11.8)

* MMF = mycophenolate mofetil; 95% CI = 95% confidence interval; IQR = interquartile range; PROMIS = Patient-Reported Outcomes Measurement Information System.
† $P = 0.01$ for MMF + pegloticase versus placebo + pegloticase.
‡ 19 patients were assessed.
§ 4 patients were assessed.
¶ Higher scores on pain intensity indicate greater severity and lower scores on physical function indicate greater severity.
# Range 0–10, with 10 indicating worst imaginable pain.
** Range 0–96, with higher scores indicating greater severity.

Secondary outcomes. At week 24, serum urate response (a serum urate level of ≤6 mg/dl) was sustained in 68% of the participants in the MMF + pegloticase arm versus 30% of the participants in the placebo + pegloticase arm ($P = 0.06$) (Table 3). We found no significant differences between groups in absolute change in serum urate level from baseline to week 24, or from week 12 to week 24. Gout flares occurred in both treatment groups throughout the study period. Figure 3 details the incidence of gout flares (proportion of patients experiencing ≥1 flare) in the MMF + pegloticase arm compared to the placebo + pegloticase arm. The proportion of patients in the MMF + pegloticase arm (and for whom data were available at that particular time point) who reported flares was significantly reduced from baseline (45%) to 24 weeks (21%) ($P = 0.02$) and from 12 weeks (63%) to 24 weeks (21%) ($P = 0.01$). We found no significant temporal changes among the small group of patients who continued to receive pegloticase in the placebo + pegloticase arm. We observed no significant differences between groups with regard to the proportion of gout flares at baseline, week 12, and week 24. Finally, we found no differences between treatment arms in patient-reported pain intensity or physical function using the PROMIS instruments, and no group difference was seen in the gout-specific patient-reported GIS scales (Table 3).

DISCUSSION

Use of pegloticase is limited by the incidence of infusion reactions and loss of efficacy, which is attributed to the production of antibodies to pegloticase. Thus, modulating this antibody response with MMF as an immunomodulatory drug was appealing based on prior evidence suggesting that MMF could reduce antidrug antibodies (11,28,29). We found that short-term concomitant use of MMF with pegloticase was associated with a statistically significant and clinically meaningful improvement in the proportion of participants achieving and maintaining a serum urate level below our target and was generally well tolerated and without infusion reactions. Our primary end point of a serum urate level of ≤6 mg/dl was sustained in nearly 70% of the participants in the MMF + pegloticase arm through 24 weeks, indicating the potential for longer-term efficacy of this approach. This result suggests that longer duration of immunosuppression would be valuable to evaluate in future trials.

We found no differences in the patient-reported outcome measures, most likely related to our study design, which required subjects who met serum urate–related stopping criteria to discontinue the trial. Significantly more patients in the placebo + pegloticase arm discontinued, potentially due to anti-PEG antibody production. In

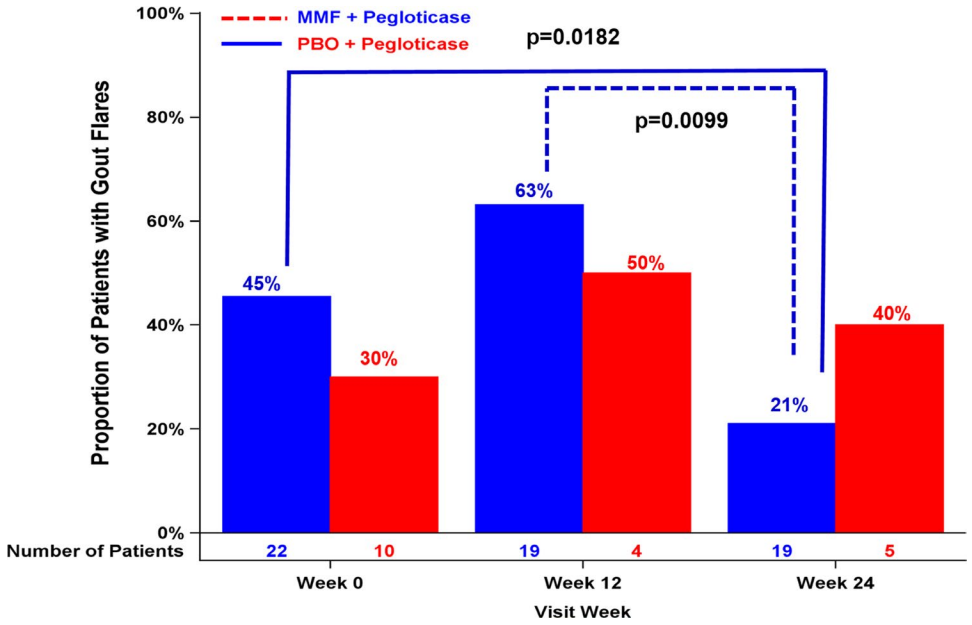

Figure 3. Proportion of patients with gout treated with mycophenolate mofetil (MMF) and pegloticase or placebo (PBO) and pegloticase who experienced gout flares over the 24-week study period. The dashed line indicates the beginning of treatment with pegloticase only. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.41731/abstract.

addition, a greater proportion of individuals in the MMF + pegloticase arm continued to experience gout flares. An increase in the incidence of gout flares over 24 weeks was not surprising, since it is well known that gout flares increase during the initiation of pegloticase, in part due to the profound lowering of urate level with pegloticase leading to mobilization of latent urate deposits (30).

Recent case series or uncontrolled observational studies with different immunomodulatory agents have suggested the potential to improve the durability of the response to pegloticase infusions, but to our knowledge, our study is the first randomized controlled trial to demonstrate this effect. In one small study, 10 patients received pegloticase biweekly along with oral MTX 15 mg weekly, and >80% of pre-infusion serum urate levels were ≤6.0 mg/dl, with no associated infusion reactions (31). A second study from a single community rheumatology practice also included a series of 10 patients who received subcutaneous MTX with a similar 80% response rate, no safety concerns, and 1 mild infusion reaction (32). Finally, the open-label Methotrexate to Increase Response Rates in Patients with Uncontrolled Gout Receiving Pegloticase (MIRROR) trial found similar results, with 11 of 14 patients who received pegloticase biweekly along with oral MTX responding (33). A case series of 10 patients showed that 70% achieved a complete response when co-treated with pegloticase and leflunomide. Finally, azathioprine was studied in combination with pegloticase, and preliminary results from an open-label trial of 12 patients demonstrated that 60% achieved a complete response without AEs; 2 patients were still receiving treatment with persistent urate-lowering therapy (34). These encouraging but inconclusive case series and some encouraging data from open-label trials led us to design a randomized, double-blind, placebo-controlled trial, which provides the advantage of minimizing bias and confounding factors seen in observational studies and allowing possible causal inference through the use of a contemporaneous control group.

While there is likely not one optimal immunomodulatory agent for use with pegloticase, MMF has strengths and limitations compared with other possible agents. Azathioprine metabolism is dependent on the thiopurine methyl transferase pathway, whereas MMF does not potentiate toxicity with concomitant use of allopurinol (which can be inadvertently administered even in patients receiving pegloticase) (35–38). Importantly, azathioprine is often less well tolerated than MMF, and requires greater dose titration (28,29,39,40). Also, in contrast to MMF, MTX requires a longer run-in time and gradual dose titration to induce clinically meaningful suppression of T and B cells (41). MTX may be problematic in patients with severe gout and multiple comorbidities (e.g., chronic kidney disease), who may commonly drink alcoholic beverages, or who demonstrate more frequent steatohepatitis, thus placing them at higher risk of side effects (e.g., folate deficiency anemia and liver dysfunction) (42,43). With MTX, and with leflunomide, there is a potential impact on liver/kidney toxicity and the possible confounding benefit of lowering serum urate and suppressing gouty attacks, effects previously reported with both agents (43–45). MMF is commonly used by rheumatologists to treat systemic lupus erythematosus, systemic sclerosis, and other connective tissue diseases. MMF has potential gastrointestinal intolerance, and in rare cases hepatorenal and/or hematologic toxicity (46–48). Of note, we did not observe such findings in the present study, although our study was significantly underpowered to detect such safety signals.

While our study has strengths in its design (i.e., a randomized, double-blind, placebo-controlled design) and our success rate in the control arm was similar to the past phase III results, which suggests some generalizability, there are limitations of our study as well (1,5,6,9). A limitation was the small sample size, as the study was designed primarily to evaluate the feasibility of concomitant MMF with pegloticase therapy. Our intent was to randomize participants in a 3:1 ratio to receive active drug versus placebo. Given the small size of the trial and the varied recruitment by site, we did not fully achieve that goal; however, the objective of unbiased assignment was maintained (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41731/abstract). Larger studies are needed to better assess the long-term safety profile of MMF immunomodulation with pegloticase.

In summary, our proof-of-concept study tested the principle that a short-term course of MMF can mitigate immunogenicity to pegloticase. To our knowledge, this is the first randomized controlled trial to demonstrate differential prolonged efficacy of pegloticase in the setting of co-administration of an immunomodulatory agent, as well as providing safety information on the combination with MMF, which was well tolerated. Furthermore, durability of response to pegloticase and a significant difference between groups at 24 weeks indicates the durability of MMF-induced immunosuppression after MMF discontinuation at 12 weeks. Our study serves as an innovative approach to customize pegloticase therapy in patients with severe gout and potentially ameliorate infusion reactions. The high personal and societal burden of chronic refractory gout mandates intensive gout management. Our clinical trial presents successful preliminary evidence for future testing of concomitant immunomodulating therapy with pegloticase in rigorously conducted investigations.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. P. Khanna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. P. Khanna, D. Khanna, Cutter, Foster, Feese, Saag.

Acquisition of data. P. Khanna, Cutter, Foster, Melnick, Jaafar, Biggers, Kuo, Feese, Kivitz, King, Shergy, Danila, Saag.

Analysis and interpretation of data. P. Khanna, D. Khanna, Cutter, Foster, Melnick, Biggers, Rahman, Kuo, Kent, Peloso, Danila, Saag.

ROLE OF THE STUDY SPONSOR

Horizon Therapeutics had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Horizon Therapeutics.

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