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Safety, Tolerability, and Efficacy of Shorter Infusion Durations of Pegloticase Administered to Patients With Uncontrolled Gout Receiving Methotrexate: AGILE Trial

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Background/Objective: Pegloticase is indicated to lower serum urate (SU) in patients with uncontrolled gout refractory to urate-lowering therapy. Pegloticase is infused for 120 minutes every 2 weeks, which can create logistical barriers. The phase 4, open-label AGILE trial (NCT04511702) assessed the safety and efficacy of shorter-duration pegloticase infusions in patients with uncontrolled gout.

Methods: AGILE examined 60-, 45-, and 30-minute intravenous pegloticase infusion durations co-administered with oral methotrexate. The desirable infusion duration was determined by enrolling patients sequentially into initial cohorts and assessing them over 24 weeks. The primary endpoint was infusion reaction (IR) incidence, including anaphylaxis. Key efficacy/safety endpoints included treatment response rate; pegloticase discontinuation due to IR; anaphylaxis, or SU-lowering response loss; and time to IR that led to discontinuation, anaphylaxis, or SU-lowering response loss.

Results: The 60-minute infusion cohort (n = 116) was chosen and enrolled based on safety reviews. Overall, 6.0% of patients (7/116; 95% CI: 2.5%–12.0%) experienced IRs, including anaphylaxis in 1.7% (2/116) of patients. A treatment response was observed in 67.2% (78/116; 95% CI: 57.9%–75.7%) of patients (SU <6 mg/dL for $\geq 80\%$ of the time during weeks 20–24). Pegloticase discontinuation due to IR, anaphylaxis, or loss of SU-lowering response occurred in 19.0% (22/116; 95% CI: 12.3%–27.3%) of patients. At least 1 adverse event occurred in 77.6% (90/116) of patients; 3.4% (4/116) of patients had serious adverse events.

Conclusions: Safety, tolerability, and efficacy results of pegloticase infused for 60 minutes were comparable to traditional infusion durations (120 min), making shorter infusion times feasible.

Key Words: anaphylaxis, infusion reaction, methotrexate, pegloticase, uncontrolled gout

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Gout is the most common form of inflammatory arthritis, affecting nearly 12.1 million adults (5.1%) in the United States.[1] Gout is conventionally treated with oral urate-lowering therapies (ULTs); however, patients are not always able to achieve adequate serum urate (SU) levels and symptom control (SU <6 mg/dL) with oral ULTs. This, coupled with reports of safety concerns and poor adherence to oral ULTs, means some patients are unable to easily achieve long-term gout remission and progress to a state where gout can quickly become uncontrolled.[2–4] Due to a variety of factors, including the inability to maintain adequate SU levels with treatment, uncontrolled gout remains undermanaged in the gout community.[5] Uncontrolled gout can have a significantly negative impact on patients' quality of life due to worsened physical function, recurrent and persistent pain, frequent gout flares, tophi deposition, and associated comorbidities.[6–8]

Pegloticase, an infused pegylated uricase enzyme, is approved by the Food and Drug Administration for the treatment of uncontrolled gout in adult patients refractory to conventional therapy.[8–10] Methotrexate (MTX) is approved for co-administration with pegloticase to decrease pegloticase immunogenicity, increase the SU-lowering response rate, and decrease infusion reaction (IR) risk.[8–11] However, the need for pegloticase infusions for a minimum of 2 hours every 2 weeks can present a high logistical treatment burden and reduce patient compliance with an effective therapy that is often a last resort for patients with refractory gout.[9,12] In patients with other chronic diseases treated with infusions, such as rheumatoid arthritis, studies demonstrate that shorter treatment infusion durations can have a positive impact on patient satisfaction, infusion clinic satisfaction, nurse satisfaction, and resource utilization.[12,13] Thus, decreasing pegloticase infusion duration may improve

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the patient experience and the efficacy of the administering center in a comparable manner. The currently recommended pegloticase infusion duration was determined for pegloticase monotherapy based on findings from a phase 3 trial.[11] However, infusion duration has not been tested when co-administered with MTX, a medication that is now recommended as a co-therapy to pegloticase.

Here, we examine the results of the AGILE clinical trial, which investigated the safety, efficacy, and tolerability of pegloticase administered for shorter infusion durations in the presence of MTX co-administration in patients with uncontrolled gout.

METHODS

AGILE (NCT04511702), a phase 4, open-label, multicenter trial, was conducted in accordance with the International Council for Harmonisation Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board (approval number 20201635) at each trial site. All patients provided written informed consent before initiating any trial-related procedures.

Patients

All patients enrolled in AGILE had uncontrolled gout, defined as SU levels ≥ 6 mg/dL on ULT, failure to maintain SU levels < 6 mg/dL with oral ULTs, and at least 1 of the following symptoms of gout: ≥ 1 tophus, ≥ 2 gout flares in the past 12 months, or gouty arthritis. Patients included in the trial discontinued all oral ULTs ≥ 7 days before MTX dosing and throughout the trial. Key exclusion criteria consisted of patients who had a serious acute bacterial infection that was not fully treated with antibiotics ≥ 2 weeks before the MTX run-in period or had a chronic bacterial infection, an MTX contraindication, glucose-6-phosphate dehydrogenase deficiency, severe renal dysfunction [estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m^2], elevated liver tests, and/or were on active treatment with immunosuppressive medications. In addition, patients with chronic liver disease, those currently receiving systemic or radiologic treatment for ongoing cancer, those with a history of malignancy within 5 years (exception: nonmelanoma skin cancer or in situ carcinoma of the cervix), those with a history of a hypoxanthine-guanine phosphoribosyl-transferase deficiency, those previously receiving treatment with pegloticase (KRYSTEXXA), another recombinant uricase (rasburicase), or concomitant therapy with a polyethylene glycol-conjugated drug, or those with a known intolerance to all protocol-standard gout flare prophylaxis regimens were excluded from the trial.

Trial Design and Infusion Duration Selection

The trial was composed of a ≤ 5-week screening period, a 4-week oral MTX run-in period, a 24-week intravenous (IV) pegloticase + MTX treatment period, and a 30-day safety follow-up as seen in Figure S1 (Supplemental Digital Content 1, http://links.lww.com/RHU/A830). Following the 4-week MTX run-in period, all patients received MTX 15 mg/wk along with 1 mg oral folic acid daily, which patients continued to receive for the duration of the treatment period. For ≥ 1 week before and throughout the treatment period, a standard gout flare prophylaxis regimen was administered in the form of colchicine and/or nonsteroidal anti-inflammatory drugs and/or low-dose prednisone (≤ 10 mg/d). A standard preinfusion prophylaxis regimen (including fexofenadine 180 mg orally, acetaminophen 1000 mg orally, and methylprednisolone 125 mg IV) was administered before each pegloticase dose. Within this preinfusion prophylaxis, corticosteroid substitution was not permitted. During the 24-week treatment period, patients were administered pegloticase 8 mg IV infusions every 2 weeks for a total of 12 infusions plus oral MTX 15 mg once weekly for up to 24 weeks.

Initial cohorts of ~10 patients were sequentially enrolled to receive 60-, 45-, or 30-minute infusions to determine the most desirable infusion duration based on safety and tolerability. If the Safety Review Committee determined that infusion speed-limiting criteria were lower than the thresholds, patients were enrolled into the next shortest infusion duration cohort. The infusion speed-limiting criteria were met if any patient recorded any severe (grade ≥ 3) IRs or other severe adverse events (AEs) within 24 hours of pegloticase infusion that were attributed to the infusion and not any other underlying disease process. An enrollment of ~110 patients was planned for the chosen infusion cohort (full enrollment cohort), where further safety and tolerability assessments were conducted. Patients with SU measurements > 6 mg/dL at 2 consecutive trial visits beginning with the week 2 visit were discontinued from pegloticase therapy but remained in the trial for follow-up visits. Patients who did not tolerate the MTX 15 mg dose during the run-in period were discontinued. During the treatment period, however, patients who did not tolerate the MTX 15 mg received a reduced MTX dose at the discretion of the sponsor medical monitor.

Endpoints

The primary endpoint was the incidence of pegloticase-related IRs (including anaphylaxis) from day 1 to week 24 in the full enrollment cohort (most desirable infusion duration). The key efficacy secondary endpoint observed in the chosen infusion duration group was the treatment response rate: patients were responders if they maintained an SU level < 6 mg/dL for at least 80% of the sampling time during weeks 20, 22, and 24. The key safety secondary endpoints were the rate of pegloticase discontinuation due to IR, anaphylaxis, or SU response loss, defined as 2 consecutive preinfusion SU levels > 6 mg/dL after week 2, and the time to an IR leading to discontinuation of treatment, anaphylaxis, or SU response loss. Other safety endpoints assessed the incidence of IRs and anaphylaxis, gout flares, major adverse cardiovascular events, time to IR, and treatment-emergent AEs (TEAEs). IR and anaphylaxis events were adjudicated by an external committee, whereas safety was monitored through AE reporting, physical examination, and laboratory value monitoring (including blood cell counts, urinalysis, liver function, and renal function tests).

Pharmacokinetic (PK) and immunogenicity exploratory endpoints included preinfusion and postinfusion PK concentrations of pegloticase and antidrug antibody (ADA) measurements, including both antiuricase and anti-polyethylene glycol (anti-PEG) antibodies. Both PK and ADA measurements were performed on day 1 and weeks 2, 6, 12, 20, and 24, with ADA measurements also collected at the 3-month post-treatment follow-up visit.

Statistical Analysis

Endpoint analyses included all patients who received ≥ 1 pegloticase infusion (safety analysis set and modified

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intent-to-treat [mITT] analysis set). The primary endpoint was met if the upper bound of the 2-sided 95% CI for the proportion of patients with pegloticase-related IRs (including anaphylaxis) was $<13\%$, a prespecified threshold. The 95% CI was calculated using a Clopper-Pearson exact method. A composite safety endpoint of discontinuation caused by IRs or anaphylaxis or meeting SU discontinuation criteria was analyzed by the Kaplan-Meier method. For the key secondary efficacy endpoint of treatment response rate, patients were classified as nonresponders if they had SU response loss (2 consecutive preinfusion SU levels >6 mg/dL after week 2) at any time through week 24, or if they had fewer than 2 SU results from separate visits between weeks 20 and 24. All endpoints were summarized with descriptive statistics, and no statistical testing was performed.

Based on the MIRROR randomized controlled trial (MIRROR RCT; NCT03994731), a previous trial of pegloticase given as 120-minute infusions co-administered with MTX compared with pegloticase monotherapy, ~5% of patients administered pegloticase + MTX were expected to experience an IR (including anaphylaxis).[8] To rule out a high IR rate, a sample size of 110 patients in the selected cohort was planned. If the IR rate was 5%, there was a $\geq 80\%$ probability that the 2-sided 95% CI upper bound for the IR rate was below 13%.

RESULTS

Determination of Optimal Infusion Duration: Initial Cohort Enrollment

To determine the optimal infusion duration based on safety and tolerability, the initial cohorts were enrolled sequentially as described above (see Trial Design and Infusion Duration Selection section). Initially, the 30-minute infusion duration was selected for further enrollment; however, the incidence rate of IRs was 12.9% in an interim review of data from 62 patients and was higher than the IR rate observed in the MIRROR RCT (4.2% in 96 patients).[8] Given the higher IR rate in the 30-minute cohort, the 60-minute cohort was chosen as the most desirable infusion duration that would be efficacious while maintaining safety and tolerability. The primary findings presented here focus on the 60-minute cohort.

Patient Characteristics of the Full 60-minute Cohort

A total of 116 enrolled patients received pegloticase in the 60-minute infusion duration cohort and formed the mITT analysis set. Of the 116 patients, 96 (82.8%) completed the trial. The median duration of pegloticase exposure was 155 days. Most patients at baseline were male (89.7%), with a mean age of 55.2 years and a mean body mass index of 33.6 kg/m^2. The mean duration since first gout diagnosis was 12.0 years, with a majority (66.4%; 77/116) of patients reporting prior or current tophi. At baseline, patients reported a mean number of acute gout flares of 7.0 and mean SU levels of 8.7 mg/dL within the past 12 months. The mean eGFR in the 60-minute cohort was 76.5 mL/min/1.73 m^2. Before the trial, 95.7% (111/116) and 21.6% (25/116) of patients had previously been prescribed allopurinol and febuxostat, respectively, for ULT (Table S1, Supplemental Digital Content 1, http://links.lww.com/RHU/A830). A total of 84.5% (98/116) and 19.0% (22/116) of patients did not exhibit improvements in SU levels or symptoms on allopurinol and febuxostat, respectively, while 11.2% (13/116) and 2.6% (3/116) exhibited an intolerance or contraindication to their respective treatment.

Overall, 111/116 (95.7%) patients reported a medical condition at baseline, with the high-risk conditions being hypertension (68/116, 58.6%), hyperlipidemia (23/116, 19.8%), osteoarthritis (22/116, 19.0%), gastroesophageal reflux disease (20/116, 17.2%), chronic kidney disease (9/116, 7.8%), nephrolithiasis (5/116, 4.3%), atrial fibrillation (5/116, 4.3%), hypothyroidism (5/116, 4.3%), and deep vein thrombosis (2/116, 1.7%; Table S2, Supplemental Digital Content 1, http://links.lww.com/RHU/A830). The baseline characteristics of the AGILE population in the 60-minute cohort were generally similar to those of the MIRROR RCT 120-minute infusion group.[8] Baseline characteristics of the MIRROR RCT pegloticase + MTX 120-minute infusion group (mITT) are shown alongside the AGILE mITT population in Table 1.[8]

During the trial, the most commonly reported concomitant medications (other than folic acid) included colchicine (66/116, 56.9%), ibuprofen (40/116, 34.5%), lisinopril (26/116, 22.4%), amlodipine (20/116, 17.2%), and atorvastatin (19/116, 16.4%). A small number of patients were also taking concomitant medications that could yield hypouricemic effects, including allopurinol (23/116, 19.8%),

TABLE 1. Baseline Characteristics of Patients in the AGILE Trial and MIRROR RCT (mITT Analysis Set)

	AGILE Trial 60-min Infusions (n = 116)	MIRROR RCT[8] 120-min Infusions (n = 96)
Sex, n (%)		
Male	104 (89.7)	88 (91.7)
Female	12 (10.3)	8 (8.3)
Age, y, mean (SD)	55.2 (11.3)	56.0 (12.5)
BMI, kg/m^2, mean (SD)	33.6 (6.3)	32.8 (5.6)
eGFR,[a] mL/min/1.73 m^2, mean (SD)	76.5 (19.4)	69.3 (17.8)
Gout history,[b] y, mean (SD)	12.0 (10.4)	13.7 (10.7)
Prior or current tophi, n (%)	77 (66.4)	74 (77.1)
No. of acute gout flares in prior year, mean (SD)	7.0 (7.1)	10.5 (13.0)
SU, mg/dL, mean (SD)	8.7 (1.7)	8.8 (1.6)

All mITT patients received ≥ 1 pegloticase infusion (8 mg every 2 wk) + oral MTX (15 mg/wk).

[a]eGFR was calculated using the MDRD equation using race and sex modifiers. Baseline is the last observation before the first dose of MTX.

[b]Time since first gout diagnosis (years).

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; min, minute; mITT, modified intent-to-treat; MTX, methotrexate; RCT, randomized controlled trial; SU, serum urate.

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TABLE 2. Primary and Key Secondary Endpoints

	60-min Pegloticase Infusions (n = 116)
Overall infusion reaction rate[a]	7 (6.0)
Infusion reaction	5 (4.3)
Anaphylaxis	2 (1.7)
Treatment response rate[b]	78 (67.2)
Pegloticase discontinuation due to infusion reaction, anaphylaxis, or treatment response loss[c]	22 (19.0)
Infusion reaction leading to pegloticase discontinuation	4 (3.4)
Anaphylaxis	2 (1.7)
Loss of SU-lowering response[d]	19 (16.4)

Data are presented as n (%).
[a]Primary endpoint (includes anaphylaxis; safety analysis set).
[b]Key secondary efficacy endpoint (mITT analysis set). Treatment response rate was defined as SU < 6 mg/dL for ≥ 80% of the time during month 6 (weeks 20–24).
[c]Key secondary safety endpoint (safety analysis set). One patient experienced both an infusion reaction leading to pegloticase discontinuation and a loss of SU-lowering response but was only counted once in the total.
[d]Loss of SU-lowering response (2 consecutive visits with preinfusion SU > 6 mg/dL).
min indicates minute; mITT, modified intent-to-treat; SU, serum urate.

losartan (16/116, 13.8%), febuxostat (4/116, 3.4%), fenofibrate (1/116, 0.9%), and colchicine/probenecid (1/116, 0.9%; Table S3, Supplemental Digital Content 1, http://links.lww.com/RHU/A830).

Primary and Key Secondary Endpoints in the Full 60-minute Cohort

Overall, the primary endpoint of IR rate (percentage of patients experiencing adjudicated IRs, including anaphylaxis) through 24 weeks of treatment was 6.0% (7/116; 95% CI: 2.5%–12.0%) in the 60-minute cohort. Overall, 1.7% of patients (2/116) experienced anaphylaxis (Table 2). As the upper bound of the 95% CI of the IR rate was less than the prespecified threshold (13%), the primary endpoint was met. In comparison, the MIRROR RCT 120-minute infusion trial had an IR rate at week 24 of 4.2% (4/96) in patients receiving pegloticase + MTX, which included 1 (1.0%) patient who experienced anaphylaxis.[8]

Treatment response rate during month 6, the key secondary efficacy endpoint, was 67.2% (78/116; 95% CI: 57.9%–75.7%) and comparable to the observed response rate in the MIRROR RCT mITT population (74.0%).[8] For the key secondary safety endpoint, 22 patients (19.0%; 95% CI: 12.3%–27.3%) discontinued pegloticase before week 24 due to an IR [n = 4; anaphylaxis (n = 2)] and/or loss of SU-lowering response (n = 19; Table 2). One patient experienced both an IR that led to pegloticase discontinuation and an SU-lowering response loss and was therefore only counted once. IR/anaphylaxis symptoms were consistent with those previously reported in the MIRROR RCT at week 24.[8] The median time to first IR that led to premature pegloticase discontinuation, an anaphylactic reaction, or loss of SU-lowering response was 17.0 days among patients who experienced an event. The median time for the composite safety endpoint was not estimable using Kaplan-Meier methods due to a low number of patients with events.

Post hoc subgroup analyses of IR and SU response rates by baseline ADA status and eGFR as a covariate for SU response were conducted. The IR rate (including anaphylaxis) for patients who were anti-PEG positive and anti-PEG negative at baseline was 5.5% (5/91) and 8.3% (2/24), respectively. The IR rate was slightly higher in the anti-PEG–negative group, but the overall number of events was low. All IRs occurred in patients younger than 65 years of age, with a rate of 7.8% versus 0% in those 65 years or older. The month 6 SU response rate (95% CI) in patients who were anti-PEG positive and anti-PEG negative at baseline was 64.8% (54.1, 74.6) and 79.2% (57.9, 92.9), respectively. eGFR was not found to be a significant covariate for SU response.

TABLE 3. AEs Occurring in ≥ 3% of Patients, AEs of Special Interest, and Serious AEs (Safety Analysis Set)

	MTX Run-in All Patients (N = 215)	Pegloticase + MTX 60-min Cohort (n = 116)
≥ 1 AE	**103 (47.9)**	**90 (77.6)**
Gout flare	74 (34.4)	77 (66.4)
Infusion reaction[a]	—	7 (6.0)
Anaphylaxis[a]	—	2 (1.7)
Infections/ infestations	9 (4.2)	21 (18.1)
COVID-19	2 (0.9)	5 (4.3)
GI disorder	13 (6.0)	13 (11.2)
Nausea	6 (2.8)	4 (3.4)
Hypertension	0	4 (3.4)
Arthralgia	1 (0.5)	4 (3.4)
Back pain	0	4 (3.4)
Peripheral swelling	0	4 (3.4)
Major adverse cardiac event[a]	0	0
≥ 1 Serious AE	**1 (0.5)**	**4 (3.4)**
Positional vertigo	0	1 (0.9)
Small intestinal obstruction	0	1 (0.9)
Infusion reaction	0	1 (0.9)
Muscular weakness	0	1 (0.9)
COVID-19	0	1 (0.9)
Gastroenteritis	1 (0.5)	0
Sepsis	1 (0.5)	0
Shigella infection	1 (0.5)	0

Data are presented as n (%).
[a]Adjudicated AE of special interest.
AE indicates adverse event; COVID-19, coronavirus disease 2019; GI, gastrointestinal; min, minute; MTX, methotrexate.

Adverse Events

In the 60-minute cohort, 77.6% (90/116) of patients experienced ≥ 1 TEAE, and 3.4% (4/116) of patients experienced ≥ 1 serious AE (Table 3). The most reported TEAE in the 60-minute cohort was gout flare, which occurred in 66.4% (77/116) of patients (Table 3). Other TEAEs included coronavirus disease 2019 (COVID-19; 5/116, 4.3%), nausea, hypertension, and arthralgia (all 4/116, 3.4%). Overall, 45.7% (53/116) of patients experienced TEAEs that were deemed related to pegloticase. The serious TEAEs reported were positional vertigo, small intestinal obstruction, IR, muscular weakness, and COVID-19; the serious IR was determined by the investigator to be related to pegloticase. During the MTX run-in period, 47.9% (103/

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TABLE 4. PK and ADA Data (PK Analysis Set)

	60-min Infusions (n = 116)
PEG trough concentration, μg/mL, median (Q1, Q3)	
Week 12	2.12 (1.50, 2.68)
Week 24	2.63 (1.95, 3.16)
PEG peak concentration, μg/mL, median (Q1, Q3)	
Day 1	2.85 (2.26, 3.59)
Week 12	4.49 (3.37, 4.94)
Anti-PEG antibody positivity	
Baseline, n (%)	91[a] (79.1)
Any postbaseline visit, n (%)[b]	57[a] (49.6)
Time to positive anti-PEG antibodies, d, median (95% CI)	44.0 (41.0–86.0)
Antiuricase antibody positivity	
Baseline, n (%)	0[a] (0)
Any postbaseline visit, n (%)[b]	29[a] (25.2)
Time to positive antiuricase antibodies, d, median (95% CI)	Not estimable[c]
Total serum MTX polyglutamate concentration, nmol/L, median (Q1, Q3)	
Day 1	49.1[d] (36.2, 70.2)
Week 24	68.1[e] (40.3, 96.9)

[a]Total n = 115.
[b]Included week 24 and post-treatment 3-month follow-up.
[c]The treatment-emergent antiuricase ADA-positive "n" is too low to obtain the median using the Kaplan-Meier method and therefore is not estimable.
[d]Total n = 108.
[e]Total n = 63.
ADA indicates antidrug antibody; min, minute; MTX, methotrexate; PEG, polyethylene glycol; PK, pharmacokinetic; Q1, quartile 1; Q3, quartile 3.

215) of patients experienced ≥1 TEAE, 9.3% (20/215) of these patients experienced TEAEs related to MTX, and 1 patient reported experiencing serious TEAEs (gastroenteritis, sepsis, and *Shigella* infection). There were no deaths reported in this trial.

Pharmacokinetics and Immunogenicity

Pegloticase and MTX Concentrations

Median pegloticase trough (preinfusion) and peak (postinfusion) concentrations at week 12 were 2.12 μg/mL [quartile 1 (Q1), quartile 3 (Q3): 1.50, 2.68 μg/mL] and 4.49 μg/mL (Q1, Q3: 3.37, 4.94 μg/mL), respectively (Table 4). These pegloticase median trough and peak concentrations in the 60-minute cohort were higher than those observed in the MIRROR RCT at week 14 [C_{min}: 1.32 μg/mL (Q1, Q3: 0.73, 1.74 μg/mL); C_{max}: 3.01 μg/mL (Q1, Q3: 1.94, 3.98 μg/mL)].[8] Serum pegloticase concentrations in the 60-minute pegloticase + MTX cohort are summarized in Table S4 (Supplemental Digital Content 1, http://links.lww.com/RHU/A830).

MTX polyglutamate levels were within the expected range for a 15 mg/week oral MTX dose, suggesting compliance with MTX administration (Table 4).[8]

Pegloticase Immunogenicity

Anti-PEG antibodies were detected at baseline in 79.1% (91/115) of patients in the 60-minute cohort (Table 4). The proportion of treatment-emergent anti-PEG–positive patients at any postbaseline visit was 49.6% (57/115; defined as ADA negative at baseline [or no baseline measurement] and ADA positive for the postbaseline assessment, or ADA positive at baseline and a ≥4 times increase in titer for the postbaseline assessment). Notably, patients who were treatment-emergent anti-PEG positive had an increased IR rate of 8.8% compared with those who were treatment-emergent anti-PEG negative (3.4%; defined as ADA negative at all assessments or ADA positive at baseline without a ≥4 times increase from baseline titer), although the total number of patients with an event was small. Overall, 6/7 patients who experienced an IR, including anaphylaxis, were nonresponders at month 6 and had high anti-PEG titers ranging from 1:1280 to 1:81,920 at IR. Patients who were treatment-emergent anti-PEG positive had a lower treatment response rate (49.1%; 28/57; 95% CI: 35.6–62.7) than patients who were treatment-emergent anti-PEG negative (86.2%; 50/58; 95% CI: 74.6–93.9). The time to the development of treatment-emergent positive anti-PEG antibodies is shown in Figure 1A.

Antiuricase antibodies were not detected at baseline in the safety analysis set; however, 25.2% (29/115) of patients in the 60-minute cohort developed treatment-emergent antiuricase antibodies during the study (Table 4). Patients who were treatment-emergent antiuricase positive had a treatment response rate of 58.6% (17/29; 95% CI: 38.9–76.5), whereas patients who were treatment-emergent antiuricase negative had a treatment response rate of 70.9% (61/86; 95% CI: 60.1–80.2).

Effect of Treatment-emergent Anti-PEG Antibodies on Pegloticase PK

Pegloticase C_{min} and C_{max} in the 60-minute cohort were impacted by the presence of treatment-emergent anti-PEG antibodies; lower median pegloticase concentrations were observed in treatment-emergent anti-PEG ADA-positive patients at steady state after week 6 compared with anti-PEG ADA-negative patients (Figs. 1B, C). Given the low titers of positive antiuricase antibodies and lack of clinical impact of these antibodies on IR and response rates, an assessment of PK by antiuricase antibody status was not performed.

DISCUSSION

The safety and efficacy of pegloticase co-administered with MTX were previously established in the MIRROR RCT.[8] However, the need to administer pegloticase for 120 minutes every 2 weeks can be a treatment and compliance barrier for patients. The current AGILE trial was designed to find an optimal shorter infusion time for pegloticase administration that is safe and effective and likely to minimize treatment barriers.

The results demonstrated that pegloticase administered at a shorter infusion duration of 60 minutes and co-administered with MTX in patients with uncontrolled gout was efficacious, with a majority of patients achieving a successful treatment response. Notably, the rate of IRs and anaphylaxis and the incidence of AEs with the 60-minute pegloticase infusion were comparable to those reported in the MIRROR RCT at week 24 (120-min infusion).[8] Similarly, no major differences in safety or efficacy were observed between subgroups, with the exception of age. However, it should be noted that due to the small number of patients experiencing an IR, definitive conclusions cannot be drawn. In addition, the current trial is too small to meaningfully adjust for these demographic features. Overall,

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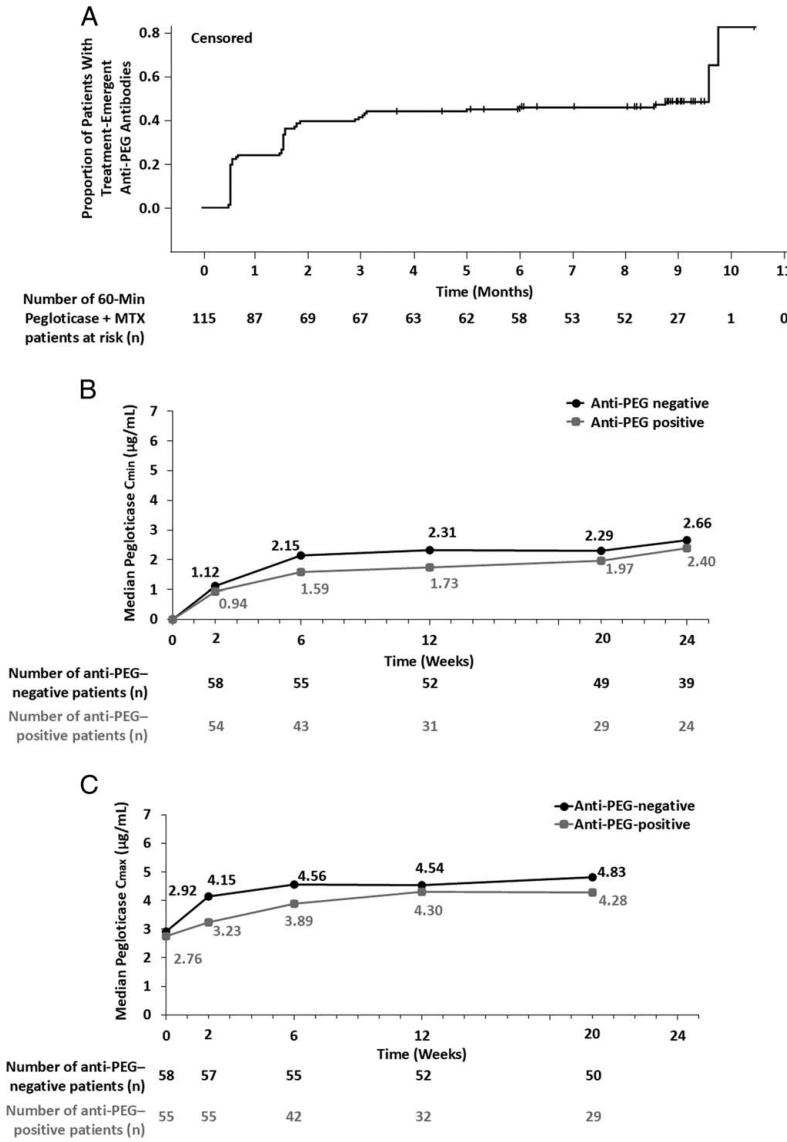

FIGURE 1. A, Kaplan-Meier curve for time to treatment-emergent positive anti-PEG antibodies. Pegloticase (B) trough (C_{min}) and (C) peak (C_{max}) concentrations over time by treatment-emergent anti-PEG status. Treatment-emergent positive is defined as ADA negative at baseline (or no baseline) and ADA positive for at least 1 postbaseline assessment, or ADA positive at baseline and a $\geq$4 times increase in titer for at least 1 postbaseline assessment. The reference time is the start time of the first pegloticase infusion. Patients who did not have treatment-emergent positive antibodies were censored on the date of the last ADA collection visit. ADA indicates antidrug antibody; anti-PEG: anti-polyethylene glycol; C_{max}, maximum concentration; C_{min}, minimum concentration; min: minute; MTX: methotrexate.

the response rates and safety profile of pegloticase in AGILE and the MIRROR RCT were comparable, indicating that a shorter infusion duration of 60 minutes is feasible, likely resulting in a lower logistical treatment burden for the patient and infusion facility.

The exposures in AGILE with shorter infusion durations were expected to be comparable to those of the MIRROR RCT; however, a new bioanalytical method was implemented in AGILE. Differences in the PK exposures are attributed to the PK variabilities and potential changes in the assay method. A new, more sensitive ADA assay was used in AGILE, which resulted in a slightly higher treatment-emergent ADA incidence when compared with MIRROR RCT. Overall, patients who had anti-PEG antibodies at baseline or developed them postbaseline had lower response rates and higher IR rates compared with corresponding anti-PEG–negative patients. Unlike anti-PEG antibodies and consistent with prior trials,[8] the presence of antiuricase antibodies did not meaningfully impact the treatment response or IR rates. Development of anti-PEG antibodies to the pegylated portion of pegloticase has been seen in previous trials studying pegloticase monotherapy.[14] Increased anti-PEG antibody levels were seen more often in non-responders in these trials.[14] Increasing concentrations of anti-PEG antibodies can affect drug PK, reducing drug concentrations to subtherapeutic levels due to ADAs binding to the drug.[15] The reason for increased rates of IR with increased titers of anti-PEG antibodies has not been well studied, but

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the loss of treatment response tends to precede the development of IRs, with patients who experience IRs also having higher anti-PEG antibody titers.[9,10]

Although taken at different time points in their respective trials (AGILE, week 12; MIRROR RCT, week 14), the concentration of pegloticase was similar.[8] In particular, the median pegloticase peak concentrations in patients receiving pegloticase + MTX therapy in AGILE were 4.49 μg/mL postinfusion compared with 3.01 μg/mL in the MIRROR RCT.[8] These results indicate that higher concentrations of pegloticase can be achieved with a shorter infusion time of 60 minutes.

The strengths of the AGILE trial included a robust sample size similar to that of the MIRROR RCT (116 and 96 patients in the mITT populations, respectively).[8] The AGILE trial also had limitations. This multicenter trial was conducted solely in the US, which limits its generalizability to a global population. The AGILE trial period was designed for 6 months of pegloticase + MTX treatment, limiting the ability of the study to report on the maximum benefit a patient could achieve with longer-term treatment compared with the MIRROR RCT's duration of 12 months.[8] Lastly, AGILE was an open-label trial without a control arm, thereby limiting the ability to directly compare efficacy between infusion durations.

In conclusion, the AGILE trial demonstrated comparable safety and efficacy of pegloticase + MTX co-therapy when pegloticase infusion duration was shortened from 120 minutes (currently used in practice) to 60 minutes. The primary endpoint of the trial (incidence of IRs including anaphylaxis) was met. The feasibility of a shorter 60-minute pegloticase infusion can lead to lower treatment burden, increased clinic staff and infusion center efficiency, and an overall improved patient experience.

KEY POINTS

- Pegloticase is an infused pegylated uricase enzyme approved for the treatment of uncontrolled gout in adult patients refractory to conventional therapy; methotrexate (MTX) co-administration is recommended to reduce the immunogenicity of pegloticase.
- Current recommended pegloticase infusion times (every 2 wk for 2 h) can impose a high logistical burden on patients.
- A 60-minute pegloticase infusion duration, when co-administered with MTX, was well tolerated and demonstrated a safety and efficacy profile comparble with 120-minute infusions, thus indicating the feasibility of a shorter pegloticase infusion for an improved patient treatment experience.

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REFERENCES

1. Yokose C, McCormick N, Lu N, et al. Trends in prevalence of gout among US Asian adults, 2011-2018. *JAMA Netw Open*. 2023;6:e239501.
2. Botson JK, Baraf HSB, Keenan RT, et al. Expert opinion on pegloticase with concomitant immunomodulatory therapy in the treatment of uncontrolled gout to improve efficacy, safety, and durability of response. *Curr Rheumatol Rep*. 2022;24:12–19.
3. Francis-Sedlak M, LaMoreaux B, Padnick-Silver L, et al. Characteristics, comorbidities, and potential consequences of uncontrolled gout: an insurance-claims database study. *Rheumatol Ther*. 2021;8:183–197.
4. Rasmussen C, Larsen JW, Christensen HM, et al. Optimising gout treatment: insights from a nurse-led cohort study. *RMD Open*. 2024;10:1–9.
5. Lee ZC, Santosa A, Khor AYK, et al. The Singapore experience with uncontrolled gout: unmet needs in the management of patients. *Cureus*. 2023;15:e36682.
6. Becker MA, Schumacher HR, Benjamin KL, et al. Quality of life and disability in patients with treatment-failure gout. *J Rheumatol*. 2009;36:1041–1048.
7. Richette P, Bardin T. Gout. *Lancet*. 2010;375:318–328.
8. Botson JK, Saag K, Peterson J, et al. A randomized, placebo-controlled study of methotrexate to increase response rates in patients with uncontrolled gout receiving pegloticase: primary efficacy and safety findings. *Arthritis Rheumatol*. 2023;75:293–304.
9. KRYSTEXXA (pegloticase) injection, for intravenous use. Package insert. Horizon Therapeutics USA, Inc.; 2012. Accessed June 20, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125293s034lbl.pdf
10. Botson JK, Saag K, Peterson J, et al. A randomized, double-blind, placebo-controlled multicenter efficacy and safety study of methotrexate to increase response rates in patients with uncontrolled gout receiving pegloticase: 12-month findings. *ACR Open Rheumatol*. 2023;5:407–418.
11. Sundy JS, Baraf HS, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA*. 2011;306:711–720.
12. Daniel SR, McDermott JD Jr, Le C, et al. A real-world, multisite, observational study of infusion time and treatment satisfaction with rheumatoid arthritis patients treated with intravenous golimumab or infliximab. *J Med Econ*. 2018;21:724–731.
13. Sehn LH, Donaldson J, Filewich A, et al. Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. *Blood*. 2007;109:4171–4173.
14. Lipsky PE, Calabrese LH, Kavanaugh A, et al. Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout. *Arthritis Res Ther*. 2014;16:R60.
15. Guttmann A, Krasnokutsky S, Pillinger MH, et al. Pegloticase in gout treatment - safety issues, latest evidence and clinical considerations. *Ther Adv Drug Saf*. 2017;8:379–388.

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