Pegloticase: a new biologic for treating advanced gout

Although pharmacologic therapies for hyperuricemia in patients with gout have been well established and are reasonably effective, a small proportion of patients are refractory to treatment and/or present with articular disease so severe as to render standard treatments inadequate. Pegloticase, a PEGylated mammalian urate oxidase with a novel mechanism of action, was recently approved in the USA for the treatment of chronic gout in adult patients refractory to conventional therapy. This paper outlines the development of this unique agent and provides details of the Phase III clinical trial program. A discussion of patient selection, treatment considerations, and risk management for infused pegloticase follows. As a new class of biologic agent offering documented and dramatic effects on lowering serum uric acid and remarkably rapid outcomes in resolving tophi, pegloticase can provide safe and effective management of hyperuricemia and gout for many patients, particularly those who have a high disease burden or who have previously failed to respond to other therapies.

KEYWORDS: biologic therapy ■ chronic gout ■ hyperuricemia ■ pegloticase

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Among the rheumatic diseases, few are as well understood as gout. The cause of gout, prolonged hyperuricemia resulting from excess production or decreased excretion of uric acid (UA), was first described by Garrod in the mid-19th century [1]. Garrod also described a semiquantitative method for measuring UA crystals in serum, commonly called the 'thread test', and wisely postulated that urate deposition was the cause of gouty inflammation. The presence of UA in renal stones and monosodium urate in tophi was documented well before that by Woolaston in 1797 [1]. Even the genetic basis of our species' susceptibility to hyperuricemia, the lack of a functional *uricase* gene, has been understood for decades.

The medical management of gout also has a long history. Hippocrates wrote that he "habitually employed purgatives in the paroxysms of gout". The control of joint inflammation with colchicine dates back centuries, and with NSAIDs and corticosteroids more than 50 years. Medical therapy to control the underlying hyperuricemia has been an integral part of gout management since the introduction of probenecid in 1951 and allopurinol in 1966 [2–4].

Yet with this age-old, comprehensive and widely accepted understanding of the management of gouty arthritis and hyperuricemia, some patients still do not fare well [5]. Furthermore, the incidence and prevalence of gout continue to rise [6].

Indeed, 100,000–300,000 of the nearly 5 million [7] patients with gout are believed to have disease that is refractory to current therapies. These patients often have a chronic, symptomatic, destructive arthropathy, frequent acute flares of joint pain and disfiguring tophaceous deposits [8]. Patients arrive at this state after widely varying clinical histories. Some patients present with disease in an atypical fashion, eluding diagnosis. Others are properly diagnosed but do not respond adequately to traditional UA-lowering therapies, are underdosed, are noncompliant or may be allergic to or intolerant of their treatment [9]. As a result of their advanced disease process, these patients have a significantly impaired quality of life (QOL) [8]. Furthermore, significant comorbidities long associated with gout, including cardiovascular disease, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease and obesity, may complicate its management [10].

Fundamental to treating patients with advanced gout is an imperative to mobilize monosodium urate deposits from articular structures and tophaceous deposits, thereby preventing joint destruction and improving function. It has been demonstrated that the more profoundly the serum uric acid (SUA) can be lowered, the more effectively tophaceous deposits can be resolved [11]. Standard therapies often take years to resolve tophi and bring chronic gouty arthropathy under control. Indeed, some propose that the treatment target for SUA in patients with gout of this severity should be well below the current standard of 6 mg/dl [12,13]. Profound

Future Medicine part of fsg

lowering of SUA would be expected to resolve the manifestations of gout in a more reasonable time frame in the severely affected patient. Recently developed urate-lowering therapies directed at the enzymatic conversion of urate to allantoin (FIGURE 1) [14–16] may accomplish this goal [8].

Current therapies targeting hyperuricemia

In September 2010, the US FDA approved pegloticase for the treatment of hyperuricemia in patients with gout who fail to normalize SUA on standard oral hypouricemic therapies and whose signs and symptoms of gout are inadequately controlled [101]. Until now, conventional therapies to treat hyperuricemia have fallen into two categories: uricosuric agents and xanthine oxidase inhibitors [12].

Uricosuric agents inhibit the renal transporter proteins URAT-1 and GLUT-9, among others, in the proximal tubule, interfering with UA resorption [17]. Probenecid is the only uricosuric drug currently available in the USA. It is not effective in patients with moderate renal insufficiency (creatinine clearance <60 ml/min). Benzbromarone, a potent uricosuric drug, is available in Europe but its use there has been limited owing to hepatotoxicity [18]. Uricosuric agents are contraindicated in patients with a history of renal stones or who only have one kidney [18].

Xanthine oxidase inhibitors decrease the UA concentration by inhibiting the enzyme responsible for the conversion of xanthine to hypoxanthine and hypoxanthine to UA in the purine degradation pathway (FIGURE 1). This results in the generation of higher concentrations of xanthine and hypoxanthine, which are more soluble than UA and are more readily cleared through the kidneys. Allopurinol, the first xanthine oxidase inhibitor, was introduced in the USA for the treatment of gout and hyperuricemia in 1966 [19]. It is the most widely prescribed xanthine oxidase inhibitor and accounts for 90% of urate-lowering therapy in the USA [18]. Allopurinol (and its primary metabolite, oxypurinol) is highly dependent on the kidney for elimination and requires dose adjustment in patients with renal impairment [18]. Allopurinol hypersensitivity syndrome, a life-threatening reaction to treatment, is a well-documented albeit rare side effect of this therapy [20].

Febuxostat, a nonpurine-selective xanthine oxidase inhibitor, was approved for the treatment of hyperuricemia and gout in Europe (2008) at doses of 80 and 120 mg daily and in the USA (2009) at doses of 40 and 80 mg daily [19]. Febuxostat is less dependent than allopurinol on renal function for its elimination, as it is primarily catabolized in the liver [12]. Current clinical knowledge concerning the efficacy of both allopurinol and febuxostat is derived largely from the Phase III febuxostat trials, which compared varying doses of febuxostat to doses ranging from 100 to 300 mg of allopurinol. These studies showed that allopurinol (300 mg daily) effectively lowered SUA to <6 mg/dl in approximately 40% of patients at their final visits, compared with approximately 40% of patients on febuxostat 40 mg daily, and 60–70% of patients on 80 or 120 mg [12,19].

Several approaches have been described to optimize urate lowering with existing oral agents. In patients with a history of allopurinol hypersensitivity syndrome, some have advocated desensitization using controlled dose escalation [21]. For patients who have tolerated allopurinol

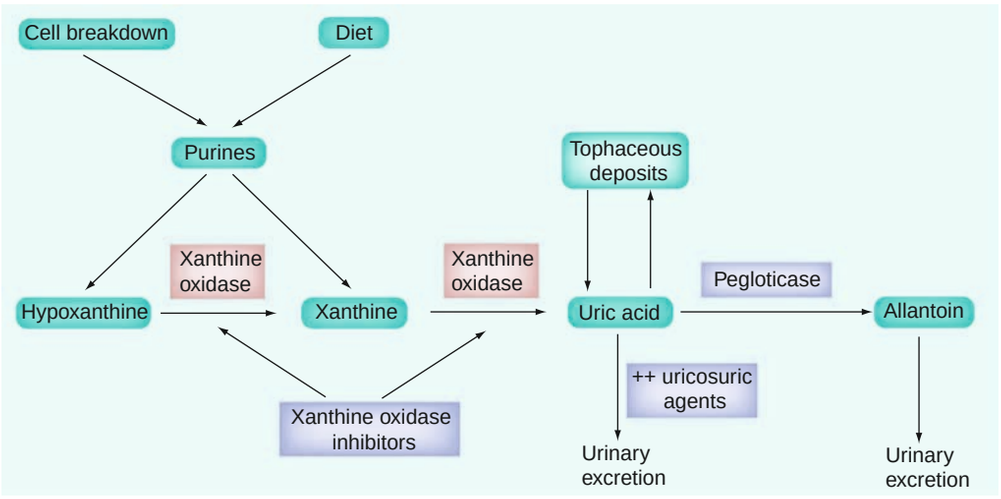

Figure 1. Therapeutic targets in urate metabolism.

therapy and are at reduced risk for hypersensitivity reactions, a carefully monitored escalation of dose above recommended levels based on creatinine clearance may be an option [22]. In patients with good (or moderately impaired) renal function, the hypouricemic effect of xanthine oxidase inhibitors may be increased by coadministration with uricosuric agents [23].

Pegloticase is the first biologic product approved for the treatment of refractory chronic gout in the USA and is the first pegylated therapeutic agent to lower UA through the enzymatic conversion of UA to allantoin (FIGURE 1). Its use is restricted to patients with severe manifestations of chronic gout who are refractory to currently available therapies [24,25]. Such patients have had few treatment options until now. Indeed, even with maximal dosing of oral UA-lowering therapies, the time to improvement of the chronic features of gout, particularly tophaceous deposits and chronic persistent synovitis, is slow, leaving patients with significant functional impairments and at risk for further complications.

Pegloticase: novel therapy for refractory chronic gout

The purine degradation pathway in most mammalian species leads to the generation of UA, which is acted upon by urate oxidase (uricase) to generate allantoin. Humans, some higher primates, and various new world monkey species lack the uricase enzyme and are susceptible to elevated serum concentrations of UA. Given its role in other species, uricase 'replacement' therapies have long been considered for the treatment of patients with severe gout. Early attempts, however, to treat this patient population with uricase extracted from different sources failed to achieve sustainable tolerability or efficacy. Rasburicase is a recombinant urate oxidase that is approved as a single dose to treat elevations in plasma uric acid (PUA) in patients at risk of tumor lysis resulting from chemotherapy [26]. Rasburicase was tested in patients with hyperuricemia and gout but its use was limited by immunogenicity and a short half-life.

Preclinical summary

Pegloticase is a recombinant mammalian urate oxidase enzyme produced by a genetically modified strain of *Escherichia coli* that has been covalently conjugated to monomethoxypoly (ethylene glycol). Pegloticase converts UA to the more soluble product, allantoin, which is then easily excreted in the urine. PEGylation increases the half-life and decreases the immunogenicity of the enzyme [3]. Age, sex, weight and creatinine clearance do not affect the pharmacokinetics of pegloticase, and therefore dose adjustment is not a concern. However, significant covariates revealed in the model for drug clearance and volume of distribution included body surface area and the presence of antipegloticase antibodies [25].

Early phase clinical experience: Phase I trial with subcutaneous administration

In an initial Phase I clinical trial, 13 patients with severe gout, including 11 with tophaceous gout and a mean baseline PUA concentration of >11 mg/dl, were treated with a single subcutaneous injection of 4–24 mg of pegloticase. The mean PUA decreased to approximately 3 mg/dl in 11 patients within 7 days. At 21 days postinjection, the mean PUA remained <6 mg/dl with doses of 8, 12 and 24 mg. It was noted that pegloticase was cleared quickly in five of the study patients and investigators hypothesized that this was owing to the presence of antibodies against the drug. Six subjects reported induration and mild-to-moderate injection-site pain within hours after the pegloticase injection, which resolved quickly. Another three patients developed a late (8–9 days postinjection) injection-site reaction with urticaria [27].

Phase I clinical experience with intravenous pegloticase

In a second Phase I study, the efficacy, immunogenicity and tolerability of a single dose of pegloticase administrated intravenously with doses ranging from 0.5 to 12 mg were evaluated in 24 patients with severe gout, including 16 with tophaceous gout. The most effective doses, based on reductions in serum urate within 24 h, were 4, 8 and 12 mg, which all produced reductions in urate levels to <2 mg/dl. The activity of pegloticase in this study was measured as the level of uricase catalytic activity in plasma and expressed as milliunits per milliliter of plasma, where 1 unit = 1 µmole of urate oxidized per min. The maximum postinfusion activity was 26 (±2.8) milliunits/ml and this reduced to 6.5 (±1.1) milliunits/ml at 21 days postinfusion. The mean plasma half-life for the uricase activity following the 8-mg dose was 12.5 (±0.9) days; plasma half-life for all doses was 9.2 (±3.2) days (range: 6.4–13.8 days). Maximal uricase activity increased linearly with pegloticase dose [28].

Antibodies against pegloticase developed in nine patients, in whom enzyme clearance was rapid, but no allergic reactions occurred. There were no severe or serious adverse events (AEs) in this study; gout flare was the most common AE, reported in 14 patients. In addition, the bioavailability, efficacy and tolerability of intravenous (iv.) pegloticase were all improved relative to the previous Phase I trial testing subcutaneous administration [29]. Based on these findings, the decision was made to move forward with further studies of pegloticase using an iv. route of administration.

Phase II dose-ranging study with iv. pegloticase

The efficacy and safety of pegloticase in adult patients with refractory chronic gout were further investigated in one Phase II and replicate Phase III clinical trials involving repeated iv. administration of the drug.

In the Phase II study, efficacy, pharmacokinetics and safety with pegloticase were assessed in gout patients who either failed to reduce serum urate to <6 mg/dl with urate-lowering therapy (allopurinol or uricosurics) or had contraindications to urate-lowering treatment. Forty one patients were randomized to undergo 12 weeks of treatment with pegloticase at one of four dosing schedules: 4 mg every 2 weeks (biweekly), 8 mg biweekly, 8 mg every 4 weeks (monthly) or 12 mg monthly. Infusions were administered over 30 min. It was shown that multiple doses of pegloticase led to substantial and sustained clinical benefits. Mean plasma urate levels were reduced to ≤6 mg/dl within 6 h in all dosage groups. UA lowering was sustained throughout the treatment period in the 8- and 12-mg groups, with the 8-mg biweekly dose providing the best balance of efficacy and safety.

The primary efficacy end point (plasma urate <6 mg/dl for 80% of the study period) was achieved in 50–88% of patients across pegloticase treatment groups. The most significant AE was gout flare (88%). Most other AEs were mild-to-moderate and unrelated to treatment according to the investigators. There were no anaphylactic reactions. Infusion-day AEs (within 24 h of the infusion) accounted for 13% of treatment-emergent AEs and occurred in 18 patients. The most common infusion-day AEs were muscle spasms, dyspnea and hypersensitivity (rash/allergic reaction/hives). Prophylaxis against infusion reactions (IRs) was not part of the treatment protocol; 12 patients who experienced infusion-day AEs were withdrawn from the study. The majority of patients (31 out of 41) developed antipegloticase antibodies, which were associated with a reduced half-life of pegloticase in some patients [29]. The hands of two patients in the Phase II trial were photographed before enrollment and at the conclusion of participation. Tophi present at the outset were documented to have resolved by the 12th week of participation [30].

Pegloticase clinical experience: Phase III trials

GOUT1 (also referred to as study C0405; n = 104) and GOUT2 (study C0406; n = 108) were two replicate, 6-month, concurrent randomized, double-blind, placebo-controlled Phase III trials of iv. pegloticase in adult patients with chronic gout refractory to conventional therapy conducted at 56 sites in the USA, Canada and Mexico [16]. Patients were randomized to receive 2-h infusions with pegloticase 8 mg either biweekly or monthly, or placebo in a 2:2:1 ratio. Patients were required to be on gout flare prophylaxis for the duration of the study with either daily colchicine or naproxen. At each infusion, patients were premedicated (fexofenadine 60 mg the night before and morning of the infusion, acetaminophen 1000 mg the morning of the infusion and hydrocortisone 200 mg immediately before the infusion). Patients who completed either of the randomized trials were eligible to enroll in a 30-month open-label extension (OLE) program.

Key inclusion criteria included baseline SUA ≥8 mg/dl; symptomatic gout with ≥three gout flares in the previous 18 months or ≥one gout tophus or chronic gouty arthritis; and a self-reported medical contraindication to allopurinol or medical history of failure to normalize UA (to <6 mg/dl) with at least 3 months of allopurinol treatment at the maximum medically appropriate dose [25].

The mean age of study subjects was 55 years (range: 23–89 years); 82% were male; mean BMI was 33 kg/m^2; mean duration of gout was 15 years; mean baseline SUA was 10 mg/dl; 73% of patients had tophi; mean self-reported flares in prior 12 months was seven [16,25]. Common comorbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), stage 3 or 4 chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%) and cardiac failure/left ventricular dysfunction (12%) [16].

The primary end point for each trial was based on a responder definition: the proportion of patients who achieved PUA <6 mg/dl for at least 80% of 16 PUA determinations during months 3 and 6. As shown in TABLE 1, significantly higher response rates were achieved in pegloticase-treated patients compared with patients receiving placebo [16,25]. Patients achieving PUA response showed sustained and profound hypouricemia during the study (FIGURE 2). In patients classified as nonresponders, mean PUA levels rose above 6 mg/dl by month 4 and did not return to below target levels [31]. Any patient who withdrew before study completion was imputed as a nonresponder [16].

Tophus response, flare incidence/frequency, tender/swollen joint counts and patient-reported outcomes were evaluated as secondary end points in the two randomized trials based on a pooled analysis (prespecified). At month 6, the percentage of patients who achieved a tophus complete response (defined as the following: 100% resolution of ≥one target tophus without the development of any new tophi or the increase in size of any existing tophi) was 45, 26 and 8%, with pegloticase 8 mg biweekly, pegloticase 8 mg monthly and placebo, respectively. The difference in tophus response between pegloticase and placebo was statistically significant for the biweekly dosing regimen (p = 0.002), but not for the monthly dosing regimen; statistical significance in the biweekly infusion group was noted as early as week 12. Significant improvements in other secondary end points, including reduction in gout flare burden, reduction in tender joints, better patient-reported QOL and functional status outcomes, were observed in pegloticase-treated patients compared with the placebo group, where no significant improvement in these outcomes was seen [16,32].

Adverse events & immunogenicity

Adverse events in randomized controlled trials

The most commonly reported serious adverse reactions in the Phase III trials were gout flares and IRs (see TABLE 2 for AEs in greater than 5% of patients with the approved biweekly pegloticase treatment). Gout flares were more frequent with pegloticase (77% in the 8-mg biweekly group) during the first 3 months of treatment compared with placebo, but by the second 3-month period, patients on biweekly therapy had fewer flares than those on placebo. This phenomenon is commonly observed upon initiation of effective uric acid-lowering therapies [33]. Prophylaxis with NSAIDs or colchicine was required before initiation of the pegloticase infusion [25].

Two cases of congestive heart failure exacerbation were reported for patients treated with biweekly pegloticase during the randomized controlled trials (RCTs; no cases were reported in the placebo arm) [25]. Physicians are advised to exercise caution and to monitor those individuals with compensated congestive heart failure who are receiving pegloticase [20]. An adjudication of cardiovascular AEs (based on end points from the Antiplatelet Trialists' Collaboration [APTC] [34]) identified three events, including two cardiovascular deaths and one nonfatal myocardial infarction in patients treated with pegloticase. All non-APTC events (three in the biweekly group and six in the monthly group vs none in the placebo group) were reported in patients with a history of cardiovascular disease. These events showed no pattern with respect to type or duration of pegloticase treatment according to

Table 1. Randomized trials primary end point results: response defined as plasma uric acid <6 mg/dl for ≥80% of the time during months 3 and 6.

Treatment group	Patients in each arm, n	Responder, n (%)	p-value
GOUT1 (C0405)			
Pegloticase 8 mg biweekly	43	20 (47%)	<0.001
Pegloticase 8 mg monthly	41	8 (20%)	0.044
Placebo	20	0 (0%)	
GOUT2 (C0406)			
Pegloticase 8 mg biweekly	43	16 (38%)	<0.001
Pegloticase 8 mg monthly	43	21 (49%)	<0.001
Placebo	23	0 (0%)	

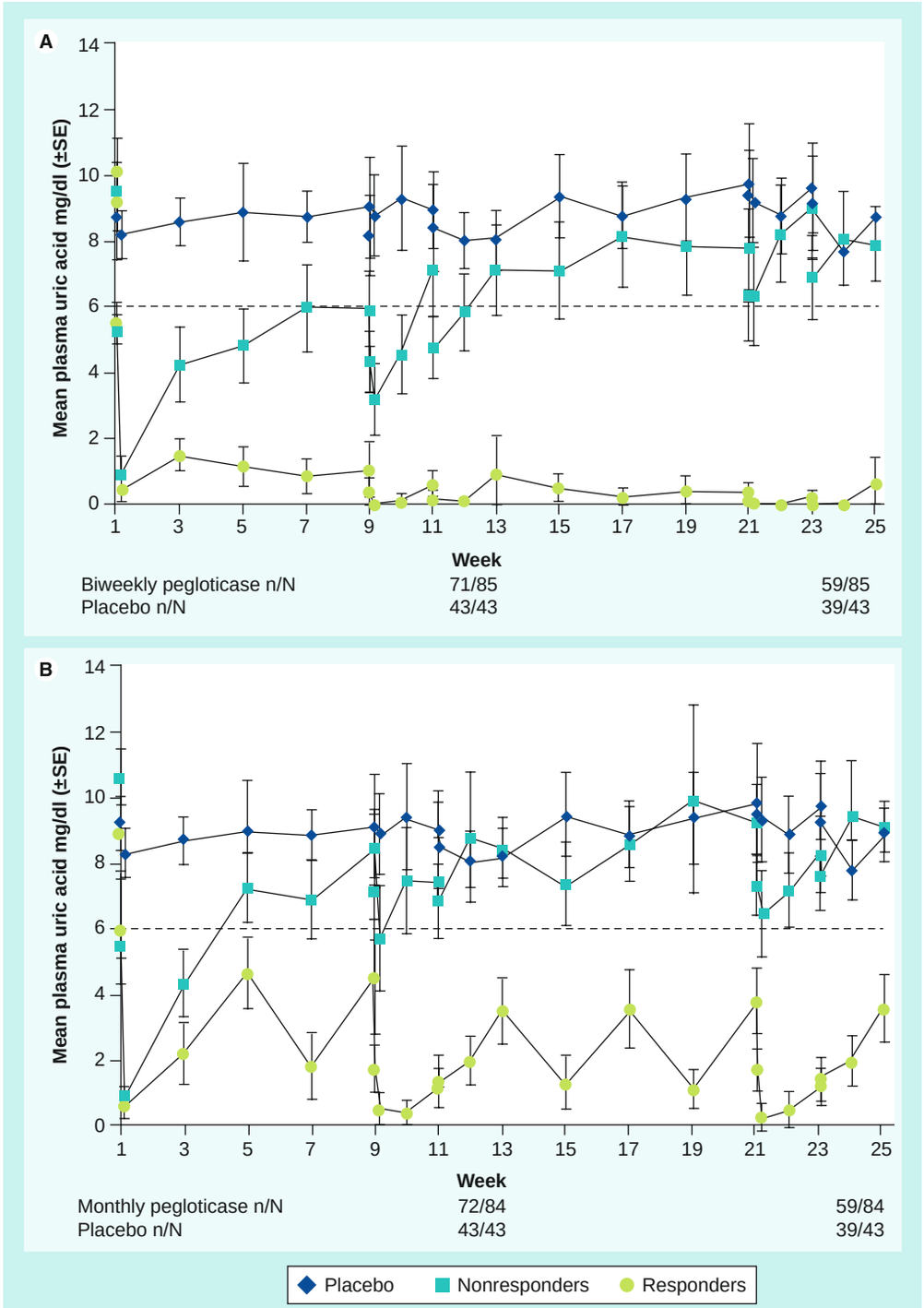

Figure 2. Uric acid over time by dose. (A) Uric acid in patients treated with biweekly pegloticase from pooled randomized trials. **(B)** Uric acid in patients treated with monthly pegloticase from pooled randomized trials.
n/N: Patients in study over total number in treatment arm; SE: Standard error.

the adjudication committee [16]. A total of seven deaths (including the two listed above) were reported between the time of randomization and closure of the study database; three for patients in the placebo arm and four for patients receiving pegloticase [16].

Infusion reactions in randomized trials

In the pooled Phase III trial population, IRs occurred in 26% of patients in the biweekly dosing regimen group and 41% of patients in the monthly dosing regimen group, compared with

Table 2. Adverse reactions occurring in ≥5% of patients treated with pegloticase compared with placebo.

Adverse reaction	Pegloticase 8 mg biweekly (n = 85), n (%)†	Placebo (n = 43), n (%)
Gout flare	65 (77%)	35 (81%)
IRs	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion‡ or ecchymosis‡	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest pain	5 (6%)	1 (2%)
Vomiting	4 (5%)	1 (2%)

†If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.
‡Most did not occur on the day of infusion and could be related to other factors (e.g., concomitant medications relevant to contusion or ecchymosis, insulin-dependent diabetes mellitus).
IR: Infusion reaction.

5% of placebo-treated patients. Serious IRs were reported in 5% of patients receiving the approved biweekly dose (and in 8% of patients in the monthly treatment cohort and in none of the placebo-treated patients) [16]. Infusion-related reactions in these trials were defined as any AE that occurred during or within 2 h after the conclusion of an infusion and that could not be reasonably ascribed to another cause. The most common of these included urticaria, dyspnea, chest discomfort, chest pain, erythema and pruritus [25]. In *post hoc* analyses of patients receiving the biweekly regimen (described below), the number of events categorized as anaphylaxis, depending upon the definition used, was three or four out of 85 [16].

Antibodies in randomized trials

Development of antipegloticase antibodies was observed in 92% of patients receiving pegloticase biweekly and 28% of patients receiving placebo in the randomized trials. This finding is consistent with other reports indicating that anti-PEG antibodies can be detected in approximately 20–25% of healthy blood donors [35]. High-titer antipegloticase antibodies were associated with a failure to maintain pegloticase-induced normalization of UA and a higher incidence of IRs [25]. Of note, a *post hoc* analysis of biweekly treatment demonstrated a low rate of IRs per total infusions in patients who maintained their PUA <6 mg/dl compared with those who did not; 0.5 versus 16% [SAVIENT, DATA ON FILE]. Importantly, for those patients reporting IRs in the biweekly pegloticase cohort, 20 out of 22 patients (91%) experienced the reaction when their UA was >6 mg/dl (TABLE 3).

Full safety review & anaphylaxis definitions

As part of their overall review of pegloticase, the FDA evaluated the risk of anaphylaxis based on the following diagnostic criteria: skin or mucosal tissue involvement, and either airway compromise and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to pegloticase or placebo injection with no other identifiable cause. Using these clinical criteria, anaphylaxis was reported in 14 (5.1%) of 273 patients studied in the total clinical program of iv. pegloticase. The frequency was similar across dosing groups, being reported in 6.5% (eight out of 123) in the biweekly cohort and 4.8% (six out of 126) in the monthly cohort. There was no report of anaphylaxis in patients receiving placebo [25].

When considering the cohort of patients receiving the approved biweekly dose of pegloticase in the Phase III trials, anaphylaxis (as defined above by the FDA) was reported in 5% (four out of 85) of patients [25]. None of these patients were hospitalized or required blood pressure support, airway protection or ventilation. Reactions resolved with cessation of infusion and, in some instances, with iv. diphenhydramine or corticosteroids. One patient received subcutaneous epinephrine (for wheezing) and another was treated with inhaled albuterol [36].

Overall anaphylaxis using clinical definition

Using a different definition, put forth by a consensus panel of the National Institute of Allergy and Infectious Disease/Food Allergy

Table 3. Frequency of infusion reactions in responders and nonresponders treated with biweekly pegloticase in randomized and open-label trials.

Treatment group	IRs (n)	Infusions (n)	%
RCT (1–24 weeks): pegloticase 8-mg infusion every 2 weeks			
Placebo	2	503	0.4
Responders	3	609	0.5
Nonresponders	40	243	16.4
OLE: pegloticase 8-mg infusion every 2 weeks			
Sustained response	3	810	0.4
Nonsustained response	44	1043	4.2[†]

[†]Amendment 3: mandated discontinuation if ≥two IRs or a severe IR.
IR: Infusion reaction; OLE: Open-label extension; RCT: Randomized controlled trial.

and Anaphylaxis Network, a retrospective analysis of IRs was performed for patients in the two randomized trials [37]. Five patients manifested signs and symptoms that met criteria for anaphylaxis: two patients in the biweekly infusion group; two patients in the monthly infusion group; and one patient who experienced a reaction at the time of their first biweekly infusion. In all instances, these reactions were judged by the investigator to be mild-to-moderate in severity [16].

Open-label extension study

Patients completing either of the Phase III trials were eligible for continued therapy in an OLE study carried out to evaluate safety and efficacy with long-term therapy. Most patients who were eligible chose to enroll (96%; 151 out of 157 eligible patients). Patients could elect active treatment at either dosing regimen or observation (n = 82 for biweekly pegloticase, n = 67 for monthly pegloticase and n = 2 for observation) for up to 30 months [38].

Among all patients treated with the approved dose of biweekly pegloticase in the OLE, 45% continued to have UA <6 mg/dl at 6 months. A total of 50 out of 60 subjects whose UA was consistently <6 mg/dl while treated with pegloticase in the randomized trials (persistent responders) maintained UA <6 mg/dl in the OLE [39].

Tophus response was associated with UA response. None of the responders in the RCT had tophus progression during the OLE, compared with 13 nonresponders who reported tophus progression during the OLE. At the end of the OLE, complete response was reported for 58% of target tophi. Among patients with tophi who were randomized to placebo in the RCT, approximately one-half (12 out of 28) had a first complete response while receiving pegloticase in the OLE [38]. The most common AEs in all treated patients in the OLE were gout flare and IRs [36]. Future publications will provide full descriptions of the OLE study and tophus response.

Overall, clinical benefits (such as progressive decrease in gout flares, reduction in the number of tender/swollen joint counts and improvements in patient-reported outcomes) observed in the randomized trials were maintained or showed further improvement during long-term pegloticase treatment [39,40].

Patient selection & treatment considerations with pegloticase

Results from the Phase III clinical trials showed that pegloticase is a potent urate-lowering agent. Sustained reductions in serum urate levels and rapid tophus resolution were observed in persistent responders with both short- and long-term therapy. UA reductions were associated with significant clinical benefit and improved patient-reported outcomes (see Figure 3).

The recommended dose and regimen of pegloticase for adult patients is 8 mg given as an iv. infusion every 2 weeks; premedication with antihistamines and corticosteroids is required [25]. One exceptional finding with pegloticase is that visible tophi can be resolved quickly within weeks to months (e.g., 22% of patients receiving biweekly pegloticase reported complete responses in less than 13 weeks) [41], compared with resolution over years for patients receiving conventional oral urate-lowering therapies [12]. As advanced gout is often associated with tophus formation and associated functional impairment and joint destruction, timely and effective resolution of tophi offers substantial benefit to patients with severe disease.

A large increase in gout prevalence has been observed in elderly patients; this has been attributed to decreased renal function, as well

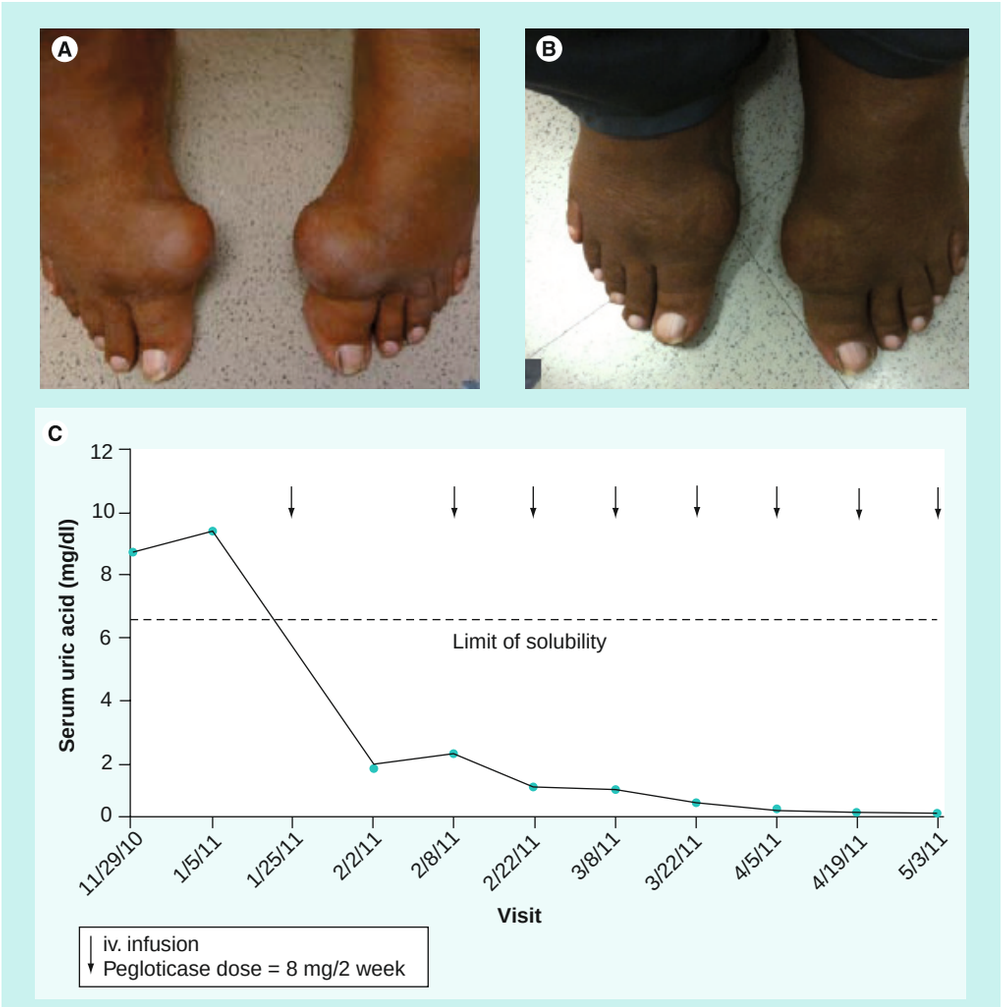

Figure 3. Tophus burden and serum uric acid levels before and after pegloticase treatment in a 69-year-old male with a 17-year history of gout previously treated with febuxostat and allopurinol with failure to lower serum uric acid below 8 mg/dl. (A) Baseline appearance of bilateral feet prior to pegloticase. **(B)** Following 14 weeks of treatment. **(C)** Uric acid levels over initial 4 months of treatment.
iv.: Intravenous.

as frequent comorbidities that promote hyperuricemia [12]. No overall differences in safety or effectiveness were observed between older and younger patients treated with pegloticase 8 mg biweekly in the randomized studies [25].

The immunogenicity of pegloticase limits its utility. High antipegloticase antibody titers were associated with loss of treatment response and a higher incidence of IRs. IRs, which are a concern with the administration of any foreign protein, were reported in 19% of patients with low or undetectable antibody titers and in over a half (60%, 31 out of 52) of patients with high antipegloticase antibody titers [16]. Importantly, loss of the pegloticase-induced urate-lowering response is a critical indicator for discontinuation of pegloticase therapy. Routine serum urate monitoring during pegloticase treatment is necessary to uncover antibody-mediated loss of response and a heightened IR risk. A *post hoc* analysis of IRs clearly showed that reactions are most likely to occur in patients who have lost their response to the UA-lowering effect of pegloticase. Indeed, it is estimated that two-thirds of IRs would be obviated by withholding therapy in a patient whose SUA rises to ≥6 mg/dl. Thus, physicians should consider discontinuing treatment if UA levels increase to above 6 mg/dl at any point in treatment, particularly when two consecutive levels above target are observed [25]. Furthermore, once UA-lowering response is lost, it is likely not to be regained and patients for whom this occurs can expect no benefit from continued treatment.

Allergic reactions, characterized as meeting diagnostic criteria for anaphylaxis in the product

label or by clinical criteria, did not require hospitalization, blood pressure support or ventilatory support. All of these reactions responded to withdrawal of therapy and simple supportive measures [25]. Mild-to-moderate IRs, when they occur, are best managed with slowing or stopping the rate of infusion and then restarting at a slower rate. More severe reactions may require treatment with antihistamine or corticosteroid therapy. From a clinical perspective, there is little to distinguish pegloticase reactions from those seen with other biologic agents commonly infused by rheumatologists.

Conclusion

Until recently, patients with advanced gout have had few options after failing conventional therapy. Pegloticase, a newly approved urate-lowering biologic agent, has demonstrated dramatic and timely benefits for patients with chronic gout by profoundly lowering SUA, resolving tophi, reducing or eliminating flares, lowering tender and swollen joint counts and improving patient-reported outcomes within 6 months. We wish to underscore the rapidity of tophus resolution (months vs years with current urate-lowering medications) [42,43] and the life-altering functional benefits realized for patients who respond to pegloticase. An OLE study demonstrated that such benefits continue for up to 2 additional years in patients responding to therapy.

The efficacy of pegloticase is limited by its immunogenicity, which first manifests as a return of UA to pretreatment levels, usually by the fourth month of therapy (and often sooner). Fortunately this is easily detected; the loss of urate lowering predicts the risk for subsequent IRs and serves as a valuable guide to terminating therapy and substantially minimizing risk. Thus, the SUA must be checked just prior to each infusion and a decision to continue treatment should be based on the result. The frequency of IRs in the RCTs was in large part a function of continuing therapy beyond the point that drug efficacy was lost and a lack of prospective awareness of the significance of the degradation of therapeutic response. Pegloticase can be safely administered by physicians familiar with the infusion of biologic therapies who are prepared to manage potential IRs. Rheumatologists who already infuse biologic response modifiers are the appropriate specialty group to do this.

Executive summary

Current management of gout

- Despite a comprehensive understanding of this disease, the management of gout remains a challenge and its incidence and prevalence continue to rise.
- Control of joint inflammation and resolution of tophaceous deposits require effective treatment of underlying hyperuricemia and are key to the management of clinically advanced gout.
- Conventional therapies that treat hyperuricemia can resolve tophi over the course of a few years.
- The speed of tophus resolution is proportional to the degree of urate lowering.
- Up to 3% of gout patients fail conventional therapy (i.e., fail to resolve clinical manifestations on standard uric acid-lowering therapies); there is a need to provide other options for this group of patients.

Refractory gout

- Refractory, or clinically advanced gout, refers to patients with a severe burden of disease who cannot maintain serum urate in a range that will resolve their clinical manifestations. The target range may be lower for these patients than the conventional 6 mg/dl. Features of advanced gout include frequent flaring, chronic arthritis and tophi, often associated with joint damage, excruciating pain and impaired quality of life.
- Significant comorbidities are frequently seen among patients with advanced gout, adding to the complexity of its management.

Pegloticase: new option for patients with advanced gout

- Pegloticase, a recombinant uricase, offers a novel means of combating hyperuricemia by catalyzing the oxidation of uric acid to allantoin, a more soluble end product, resulting in lower urate levels, less tophi and fewer symptoms.
- Pegloticase is approved in the USA for the treatment of chronic gout in adult patients refractory to conventional therapy.
- In clinical trials, treatment with pegloticase has shown efficacy and safety in a population of advanced gout patients; responders achieved sustained reductions in serum urate levels, resolution of tophi, cessation of flares, lowered numbers of tender and swollen joints and improved patient-reported outcomes.
- Patients with initial urate lowering who subsequently return to uric acid levels above 6 mg/dl when treated with pegloticase can be indentified within the first few months of treatment and discontinued.
- The most commonly reported serious adverse reactions for pegloticase from clinical trials were gout flares and infusion reactions; patients receiving pegloticase should be premedicated with antihistamines and corticosteroids prior to infusion.
- Routine serum urate monitoring during pegloticase treatment is essential to predict antibody-mediated loss of response and the risk of infusion reactions.

Pegloticase affords patients with severe clinical manifestations of chronic gout the chance for dramatic resolution of tophaceous deposits, chronic synovitis and related disabilities, along with decreased flares and improved QOL, in a shorter period of time than has previously been attainable.

Future perspective

Pegloticase is a powerful biologic agent currently indicated for the treatment of refractory chronic gout in adult patients with signs and symptoms reflecting inadequate urate control. The authors feel it may well become standard 'bridge therapy' for treating advanced gout in a larger group of patients for whom the severity of disease, irrespective of UA levels, carries unacceptable functional limitations. Given its effectiveness in resolving tophi, pegloticase may be used to dissolve crystal deposits in patients who may eventually be switched to an oral agent for maintenance treatment. Strategies to decrease its immunogenicity might help to limit toxicity and extend its efficacy to a larger proportion of treated patients.

Financial & competing interests disclosure

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