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New advances in the treatment of gout: review of pegloticase

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Abstract: Treatment-failure gout (TFG) affects approximately 50,000 patients or about 1% of the overall population of patients with gout in the United States of America. The severity of TFG is manifested by frequent acute attacks of disabling arthritis, chronic deforming joint disease, destructive masses of urate crystals (tophi), progressive physical disability, and poor health-related quality of life. Pegloticase (Krystexxa[®]; Savient Pharmaceuticals, Inc), a novel PEGylated urate oxidase (uricase) enzyme, has been resubmitted for US Food and Drug Administration approval. In a 6-month, placebo-controlled clinical trial, 8 mg of pegloticase for every 2 weeks induced a lytic decrease of serum urate (sUr) concentrations, leading to dissolution of tophi in 40% of patients at final visit. However, 58% were nonresponders to the defined target sUr of 0.36 mmol/L (80% were nonresponders during months 3 and 6), possibly due to antibody formation. Also, 26%–31% experienced infusion reactions (IRs) and 77% suffered from gout flares. Although long-term data are awaited, an anti-inflammatory strategy, eg, based on glucocorticosteroids, is needed to prevent pegloticase antibody formation leading to IRs and diminished or shortened efficacy, and might also prevent gout flares. According to the current clinical data, pegloticase might have an important role as a (bridging) treatment in sUr-responsive patients for tophi clearance in severe chronic refractory gout.

Keywords: pegloticase, hyperuricemia, gout, pharmacotherapy, PEG-uricase

Introduction

Gout is the collective name for several clinical disorders that are characterized by dysmetabolism resulting in the formation and deposition of monosodium urate (MSU) crystals. The condition is associated with the recurrent episodes of acute joint pain due to the deposition of MSU crystals in the synovial fluid. In addition to these effects observed in the joints, skin or subcutaneous tissues and kidneys may also be affected by tophaceous deposits, cellulitis, urate nephropathy, and/or kidney stones. In most cases, no identifiable underlying cause of gout is present, but metabolic factors, such as reduced renal function, obesity, and the use of diuretics or salicylates, are usually present that may contribute to accumulation of urate (uric acid) in the body. Hyperuricemia may exist for several years to decades before the first symptoms of gout attacks appear, and therefore, it is a disease associated and correlated with aging.

Gout is one of the most common inflammatory manifestations of arthritis; however, in general, it appears to be poorly managed.^{1,2} Partly, this is due to an absence of adequate treatment strategies and guidelines. In 2006, the European League against Rheumatism (EULAR) published the first international recommendations for the diagnosis and treatment of gout.^{3,4} The development of these EULAR and British Society

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for Rheumatology guidelines coincided with the improved professional and patient education and the urge for improved professional performance.^{3–5} Until recently, allopurinol was the only antihyperuricemic drug with availability worldwide (Table 1). Two uricosurics with barriers regarding availability (benzbromarone and probenecid) have been available for years, but their exact place in the treatment strategy is not clear. In 2008 and 2009, respectively, European Medicines Agency and the US Food and Drug Administration (FDA) approved febuxostat (a selective nonpurine xanthine oxidase inhibitor) for the treatment of gout, thereby making a new treatment option available.^{6,7} A new uricosuric in clinical development, RDEA594, was presented in 2010.⁸

Pegloticase (Krystexxa®; Savient Pharmaceuticals, Inc., NJ), also known as Puricase® (Duke University and Mountain View Pharmaceuticals, Inc., Menlo Park, CA) or polyethylene glycol (PEG)-uricase, has been accepted for FDA resubmission in 2010 for the treatment of patients with conventional therapy refractory gout (CRG).^{9,10} In 2009, it was not approved for treatment-failure gout (TFG) because of manufacturing issues.^{11,12} The agency also wanted more communication with prescribing doctors about safety and monitoring. Although the definition of TFG and CRG differs slightly, this review will use TFG as the indication used initially. Pegloticase was granted orphan drug designation by the FDA in 2001. In the following topics, a review is given on pegloticase and its place in current treatment strategy.

Antihyperuricemic treatment

Antihyperuricemic maintenance therapy is indicated when recurrent gout attacks (>2/y) or tophi are presented by the

patients.^{4,5,13} The treatment goal according to serum urate levels should be to achieve a sufficient negative urate mass balance to reverse the urate accumulation in the body. It is known from observational data that prevention of recurrent attacks and dissolution of tophi depend on the serum urate level that is achieved, preferably below 0.30 mmol/L (5 mg/dL).^{14–19} The rate of resorption of tophi is proportional to the lowering of serum urate achieved.¹⁸ It may take years of chronic exposure to conventional urate-lowering agents in order to completely dissolve tophi. In fact, complete resolution of tophi has never been demonstrated in a randomized controlled trial for any of the approved urate-lowering agents.

In clinical practice, attainment of target urate levels is often difficult worldwide because of the limited efficacy, tolerability, and availability of current antihyperuricemic drugs.^{20,21} Some guidelines have set the serum urate target at 0.36 mmol/L (6 mg/dL), but this may be adequate only for long-term treatment after initial “debulking” in patients with progressive disease.⁴

The most commonly used urate-lowering drug is allopurinol. However, its effectiveness is limited by a number of issues, including the need to use lower doses in patients with renal insufficiency, failure to lower serum uric acid levels sufficiently due to subtherapeutic dosing, and an adverse event (AE) profile that includes gastrointestinal, hepatic, renal, hematological, and skin toxicities that occur in an approximately 20% of patients who take this drug.^{22–29} Importantly, hypersensitivity reactions occur in 2%–4% of patients that in some instances have been fatal.³⁰ It is estimated that approximately 5% of patients are forced

Table 1 Antihyperuricemic drugs in gout

Drug	Action: indication	Daily dose: standard	Characteristics
Allopurinol orally	XO _i : all	100–900 mg: 300 mg	Dosage adjustment to renal function
Benzbromarone orally	Urate transporter: low excretor, subject to intolerance or allergy to allopurinol	50–200 mg: 100 mg	Poor efficacy in severe renal function impairment
Febuxostat orally	XO _i : all, particularly in Allo intolerance	40–120 mg: 80 mg	No dosage adjustment in renal impairment
Probenecid orally	Urate transporter: low excretor	500–2,000 mg: 1,000 mg	Poor efficacy in moderate to severe renal function
Rasburicase iv	UrO: lytic effect on tophi	Compassionate use: eg, 0.2 mg/kg in 60 min; infusion on d 1, then 1x per wk; (+methylprednisolone 100 mg iv)	Biological
Pegloticase iv	UrO: chronic refractory gout	8 mg every 2–4 wk	Biological

Abbreviations: XO_i, xanthine oxidase inhibitor; iv, intravenous; UrO, urate oxidase.

to discontinue allopurinol therapy due to the development of an AE. Febuxostat, which was approved recently and does not require dose adjustment in mild to moderate renal impairment, may provide a therapeutic alternative for patients unable to tolerate allopurinol.⁷

Special considerations when antihyperuricemic treatment is used

Antihyperuricemic drugs might provoke arthritis or induce an attack of gout because of urate mobilization. For safety reasons, antihyperuricemic therapy should be given only after the gout attack has subsided, preferably with inflammatory protection (eg, low-dose colchicine, nonsteroidal anti-inflammatory drugs, or glucocorticosteroids), which should be initiated several days to two weeks earlier and given for a period of 2–3 months usually.^{4,31} With normal renal function, administration of allopurinol, probenecid, and benzbromarone could be started, respectively, at doses of 100 mg once daily, 250 mg twice daily, and 100 mg once daily (use of benzbromarone is not approved in the United States) and could be titrated every 2 weeks to standard dosage if tolerated. After 6–8 weeks, the efficacy can be evaluated and dose can be increased if necessary (Table 2). Maintenance doses usually range as follows: allopurinol, 200–600 mg once daily; benzbromarone, 100–200 mg once daily; and probenecid, 500–1,000 mg twice daily. In case of impaired renal function, allopurinol dosage should be started at 100 or 50 mg/d (depending on the renal function), evaluated after 6–8 weeks, and titrated carefully (with 100 or 50 mg/d).

When a history of urolithiasis is present, adequate diuresis should be ensured and alkalization should be considered, especially if a uricosuric is prescribed and the urine of the patient is acidic (pH < 6.0). Compliance is also a special consideration when supervising gout patients, and it is crucial to explain the dosing schedule and any potential side effects to the patient in order to prevent early withdrawal.

TFG and chronic refractory gout

TFG is a severe outcome of progressive gout resulting from the intolerance to or refractoriness to available urate-lowering therapy to prevent urate crystal deposition by reducing and maintaining serum urate levels in a subsaturating range. TFG is characterized clinically by painful arthritis and chronic arthropathy, destructive tophi, impaired quality of life, and chronic disability. Hyperuricemia and gout are often accompanied by significant medical comorbidities, including

Table 2 Suggested, current experience-based strategy for initiation of antihyperuricemic therapy⁶

1. Confirmation of diagnosis: detect urate crystals by means of polarization microscopy
2. Two or more gout flares per year or tophi/joint destruction due to gout attacks
3. Therapeutic advice^a: allopurinol 100–300 mg/d^b
allopurinol intolerance: consider febuxostat
4. Laboratory monitoring of the effectiveness at 6–8 wk:
sUr < 0.30 mmol/L, then continue allopurinol
sUr > 0.30–0.36 mmol/L, but no further attacks (without colchicine/NSAID/corticosteroids), then continue allopurinol
sUr > 0.30 mmol/L plus gout attacks/persistent tophi and uUr > 1.5 mmol/24 h, go to 5
sUr > 0.30 mmol/L plus gout attacks/persistent tophi with uUr < 1.5 mmol/24 h, go to 6
5. Therapeutic advice: increase allopurinol (eg, +100 mg/d or double the dose); then go to 4
Allopurinol inefficacy at maximum dosage (corrected for renal function): consider febuxostat
6. Therapeutic advice: add uricosuric, eg, benzbromarone 100 mg/d or probenecid 500 mg twice daily; then go to 4
7. Laboratory monitoring of the effectiveness of sUr and uUr (possibly pH⁹) after 6 mo: see 5
8. Note: when trying to clear tophi, target value is sUr < 0.30 mmol/L.
Consider pegloticase when target value cannot be reached with conventional oral drugs or for more rapid debulking in severe bulky disease

Notes: ^aSubject to motivation and tolerance by patient; ^bSubject to calculated creatinine clearance (cCC) > 50 mL/min, if cCC < 50 mL/min, then only increase allopurinol with 100 mg/day. Serum oxipurinol concentrations might be measured in patients with renal insufficiency; ^cTarget value for sUr ≤ 0.36 mmol/L might be sufficient when there are no further gout attacks despite withdrawing colchicine/NSAID, otherwise lower target value of 0.30 mmol/L; ^dIf experiencing kidney stones or uUr > 6.0 mmol/24 hours and pH < 7.0 consider alkalinizing with sodium bicarbonate.

Abbreviations: sUr, serum urate; NSAID, nonsteroidal anti-inflammatory drug; uUr, 24-hour excretion of urate in urine.

cardiovascular disease, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, and obesity. These associated disorders are especially frequent among patients with TFG. The combination of severe gout and a high burden of cardiovascular and metabolic comorbidities, often requiring polypharmacy, makes TFG exceptionally difficult to manage.^{11,32}

TFG affects approximately 50,000 patients or about 1% of the overall population of patients with gout in the United States.¹¹ However, the prevalence may decrease with the availability of new (oral) antihyperuricemic drugs like febuxostat. The severity of TFG is manifested by frequent acute attacks of disabling arthritis, chronic deforming joint disease, destructive masses of urate crystals (tophi), progressive physical disability, and poor health-related quality of life. Several case reports describe successful (off-label) use of rasburicase in TFG.^{33–39} However, its use in gout is compromised: first, by the risk of immunologic

reactions; second, by its short half-life (18 hours) that demands an infusion every 1–2 weeks according to serum urate levels for optimal treatment efficacy; and third, by the lack of clinical experience and a dosing scheme consensus for gout.⁴⁰ Terkeltaub⁴⁰ has proposed to use uricase-based therapy in severe tophaceous gout as bridging therapy for rapid debulking of urate, whereafter a less rigorous regimen might be sufficient, while maintaining a negative urate balance.

Pharmacology

Pegloticase is intended for use in TFG at a dose of 8 mg (of uricase protein) by intravenous infusion every 2 weeks. The active substance is a genetically engineered, recombinant, PEG-conjugated mammalian (porcine-like) uricase enzyme. It metabolizes uric acid into soluble allantoin for excretion by the kidney, with hydrogen peroxide and carbon dioxide as oxidative byproducts. It is PEGylated in order to lengthen the circulating half-life of the enzymatically active uricase moiety and to lessen the immunogenicity in long-term use. Because urate, the substrate of this enzyme, is small in size, it is able to diffuse through a web of polymer molecules to reach active sites. This concept for uricase has already been described and clinically demonstrated in 1981.^{41,42}

A Phase I study investigated the pharmacokinetics, pharmacodynamics, and safety of pegloticase by single subcutaneous injection in 13 subjects with TFG.⁴³ It appeared that in 5 of 13 patients, the half-life of pegloticase was significantly lower than in the rest of the group and no measurable activity was present after 10 days, whereas in the other 8 patients, activity was still present after 21 days.⁴³ The faster clearance in these 5 patients was demonstrated to be related to the presence of IgM and IgG antibodies against pegloticase.

In a second Phase I study ($n = 24$), pegloticase was given as a single dose intravenously. The most efficacious dosage for reducing serum urate (sUr) were 4, 8, and 12 mg. The volume of distribution ranged from 5.0 to 10 L, the $t_{1/2}$ ranged from 163 to 332 hours, and C_{max} values ranged from 1.7 to 36 mU/mol (1 U = 1 μ mol urate oxidized per minute). It was also noted that the rate of terminal clearance was increased in patients in whom IgG was expressed to the pegloticase.⁴⁴

Pegloticase in clinical trials

In a Phase II clinical trial of 12 weeks ($n = 41$), patients were divided into four cohorts and received pegloticase during the 12 weeks at a dosage of 4 or 8 mg for every 2 weeks or 8 or 12 mg for every 4 weeks.^{45–47} These data demonstrate that patients treated with 8 mg of pegloticase for every 2 or

4 weeks had a lytic, ie, very rapid and sustained reduction in plasma uric acid; 4 mg for every 2 weeks was not as effective, and 12 mg for every 4 weeks did not provide additional benefit compared with 8 mg for every 4 weeks. A majority of patients developed antibodies to pegloticase; infusion reactions (IRs) appeared to be associated with the presence of an antibody response. The data also show that these patients can be categorized into two groups based upon their sUr values after repeated pegloticase treatment: 1) persistent responders (previously referred to as responders), who had a sustained reduction in sUr, and 2) transient responders (previously referred to as nonresponders), who initially had sUr values below 0.36 mmol/L but the values increased over time to above 0.36 mmol/L. Although all patients had a response after the first pegloticase administration, those patients who developed antibodies appeared to have transient responsiveness and a higher risk for IRs. Also, cases of patients experiencing profound improvements in their joint function and breakdown of existing gout tophi were reported during the 12-week trial.⁴⁸

On the basis of the safety and efficacy results of the Phase II study, the pegloticase dose selected for advancement to Phase III registration studies was 8 mg administered intravenously (diluted to 250 mL) over 120 minutes every 2 weeks or every 4 weeks.^{11,42}

Two Phase III, 6-month, randomized, double-blind trials were performed in patients with TFG: Gout Outcome and Urate Therapy (GOUT1 and GOUT2).^{49,50} TFG was defined as follows: ≥ 3 flares in previous 18 months, ≥ 1 tophus, or prevalent gouty arthropathy; sUr ≥ 8.0 mg/dL; and contraindication to or self-reported failure to control sUr with maximum medically appropriate dose of allopurinol. In total, 212 subjects received (by randomization 2:2:1) 8 mg of pegloticase (of uricase protein) for every 2 weeks ($n = 85$) or every 4 weeks ($n = 84$) or received placebo ($n = 43$). Colchicine or nonsteroidal anti-inflammatory drugs were used for gout prophylaxis. IR prophylaxis consisted of oral fexofenadine and paracetamol and hydrocortisone 200 mg intravenously before infusion. The primary efficacy end point was the percentage of sUr responders, defined as the subjects with sUr < 0.36 mmol/L $\geq 80\%$ of the time in months 3 and 6. Secondary end points assessed treatment effect on tophus size, gout flares, number of swollen and tender joints (TJs), quality of life (SF-36, physical component summary score), and disability (health-related quality of life as determined by the Health Assessment Questionnaire Disability Index [HAQ-DI]).^{51,52} Primary end point data are reported as replicate analyses; secondary end point data were pooled for GOUT1 and GOUT2.

Subjects, mean age 55 years, were mostly male (82%) and had high cardiovascular comorbidity rates. Plasma urate response was significantly higher in both pegloticase groups vs placebo group in both studies and ranged from 35%–42% vs 0% (Table 3). Complete resolution of ≥ 1 tophus occurred in 40% of pegloticase every-2-weeks patients ($P = 0.002$) and in 21% of pegloticase every-4-weeks patients (not significant vs placebo) vs 7% in placebo subjects; in 22%, tophus resolution occurred within 13 weeks.^{53–55} SF-36, HAQ-DI, and TJs improved significantly in both pegloticase groups vs placebo group.^{56,57} Incidence and frequency of gout flare were significantly higher during months 1–3 in both pegloticase groups despite prophylaxis but were significantly lower during months 4–6 in pegloticase every-2-weeks group (41%) vs placebo group (67%, $P = 0.007$). The most common AEs were flares (in 77% pegloticase every-2-weeks, 83% pegloticase every-4-weeks, 81% placebo subjects) and IRs (in 26% pegloticase every-2-weeks, 41% pegloticase every-4-weeks, 5% placebo subjects). AE discontinuations were mostly due to IRs (19/34). Serious AEs, mostly flares and IRs, occurred in 24% pegloticase every-2-weeks, 23% pegloticase every-4-weeks, and 12% placebo subjects.

In conclusion, 42% and 35% of TFG subjects on pegloticase every-2-weeks and every-4-weeks, respectively, achieved the primary efficacy end point of sUr control. This was accompanied by significant improvement in clinical outcomes. Subjects who completed the GOUT1 or GOUT2 trial were given the option to enter an open-label extension trial under a separate protocol (GOUT3).

In an update of the extension study (GOUT3), efficacy in reduction of sUr concentration and symptomatic end points were reported to be maintained with treatment extending up to 1 year.⁵⁸

Table 3 summarizes the efficacy and tolerability results of pegloticase in randomized controlled trials, which were reviewed by the FDA and some recent review articles previously.^{11,59,60}

Safety and tolerability

The FDA review of safety database for pegloticase identified concerns in three main areas: 1) a higher rate of serious cardiovascular events, 2) the occurrence of IRs and allergic reactions, and 3) immunogenicity of pegloticase with an adverse influence on efficacy and safety (Table 4).¹¹ Deaths were seen in both study arms, in 4% in the pegloticase arm vs 1% in the placebo arm, but there were no significant statistical differences.

The higher rate of serious cardiovascular events was seen in both pegloticase treatment arms and demonstrated no relation to dosage regimen. The cardiovascular events showed no particular pattern and included arrhythmias, ischemic events, and congestive heart failure. A consultation from the FDA Division of Cardiovascular and Renal Drug Products concluded that the distribution of cardiovascular deaths and cardiac severe AEs was not obviously unusual in view of the fact that it occurred in patients predisposed to such events and taking into account the unequal randomization in the clinical trials.¹¹

Table 3 Efficacy and tolerability of pegloticase in randomized controlled trials

Study	Treatment, dosage	No. of patients	Duration	sUr < 6 mg/dL (0.36 mmol/L) ^a	Gout flares	Tophus dissolution (final visit)	Withdrawal due to ADR
Phase I ⁴³	4–24 mg sc	13	single dose	–	–	–	–
Phase I ⁴⁴	0.5–12 mg iv	24	single dose	–	–	–	–
Phase II ^{45,46}	4 mg iv q2w	41	3 mo	4/7 (57.1%)	86%	Not available	15 (37%)
	8 mg iv q2w			7/8 (87.5%)	63%	Case reports ⁴⁸	
	8 mg iv q4w			7/13 (53.8%)	92%		
	12 mg iv q4w			8/13 (61.5%)	100%		
GOUT I and GOUT 2 ^{49,50}	8 mg iv q2w	43 + 42	26 wk	20/43 (46.5%) ($P < 0.001$) ^b and 16/42 (38.1%) ($P < 0.001$) ^b	mo 1–3: 77%; mo 4–6: 41% ($P = 0.007$) ^b	21/52 (40.4%)	1 (2%)
	8 mg iv q4w	41 + 43		8/41 (19.5%) ($P = 0.044$) ^b and 21/43 (48.8%) ($P < 0.001$) ^b	mo 1–3: 81%; mo 4–6: 57%	11/52 (21.2%)	16 (19%)
	Placebo	20 + 23		0/20 (0%) and 0/23 (0%)	mo 1–3: 54%; mo 4–6: 67%	2/29 (6.9%)	17 (20%)

Notes: ^aProportion of subjects maintaining a PUA concentration <6 mg/dL for at least 80% of the time during the treatment period (Phase II) or during the months 3 and 6 (Phase III); ^bPegloticase vs placebo.

Abbreviations: ADR, adverse drug reactions; PAU, plasma uric acid.

Table 4 Summary of treatment-emergent AEs including IRs and gout flares reported¹¹

Safety characteristics (No.)	GOUT 1 and 2			GOUT 3	
	Placebo (N = 43)	Pegloticase q2 wk (N = 85)	Pegloticase q4 wk (N = 84)	Pegloticase q2 wk (N = 85)	Pegloticase q4 wk (N = 84)
Adverse events (AEs)	370	693	870	1,044	1,411
Subjects with AEs	41 (95%)	80 (94%)	84 (100%)	83 (98%)	84 (100%)
Subjects with serious AEs (SAE)	5 (12%)	20 (24%)	19 (23%)	24 (28%)	27 (32%)
Subjects with infections	22 (51%)	30 (35%)	40 (48%)	41 (48%)	54 (64%)
Subjects with serious infections	4 (9%)	3 (4%)	5 (6%)	3 (4%)	7 (8%)
Subjects with malignancy	1 (2%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
Subjects with infusion reactions (IR)	2 (5%)	22 (26%)	34 (41%)	26 (31%)	38 (45%)
Subjects who discontinued due to AEs	1 (2%)	16 (19%)	17 (20%)	18 (21%)	21 (25%)
Deaths	1 (2%)	3 (4%)	1 (1%)	0 (0%)	2 (2%)

Note: Except for the “number of AEs”, subjects are counted only once in each row.

A higher proportion of patients experienced serious AEs in the pegloticase every-4-week (23%) and pegloticase every-2-week (24%) treatment groups as compared with placebo-treated patients (12%) due to the high rate of IRs seen in the pegloticase every-4-week (41%) and pegloticase every-2-week (26%) groups. A higher proportion of IRs that were experienced by the patients in the pegloticase every-4-week group (36%) was of moderate to severe intensity as compared with the pegloticase every-2-week group (18%). The occurrence of IRs peaked with the administration of dose 3 or 4 of pegloticase and declined thereafter. Pegloticase was shown to be immunogenic with 88% of patients in the pegloticase every-2-week group and 89% of patients in the pegloticase every-4-week group seroconverting to antibody positivity over the course of these studies. The magnitude of positive antibody titers to pegloticase was associated with a higher rate of IRs and a decrease in urate-lowering effects of therapy.⁶¹ Routine sUr monitoring might be used to prospectively identify patients receiving pegloticase who may no longer benefit from treatment and are at greater risk for IRs.⁶² A next generation, less immunogenic form of PEG-uricase might be developed in which uricase will be coupled to PEG lacking a methoxyl or other alkoxyl group at the terminus remote from the protein-coupling function.⁹

Because of the formation of hydroxyl peroxide by uricase, pegloticase therapy may be complicated in patients with deficiencies of glucose-6-phosphate dehydrogenase or catalase.^{63,64}

In conclusion, a strategy on prevention of immunologic responses is warranted, eg, by prescribing anti-inflammatory regimen. The same regimen may also be very useful for the prevention of gout flares because of the mobilization of urate due to the rapid urate metabolism in the circulation by pegloticase.

Summary

In 6-month, placebo-controlled clinical trials, 8 mg of pegloticase for every 2 weeks induces a lytic decrease of sUr, leading to dissolution of tophi in 40% of patients at final visit (45% in subjects treated for 25 weeks). The velocity of tophus dissolution in responders to pegloticase seems faster than combination treatment of allopurinol and benzbromarone (19.6 ± 9.1 months), which may be clinically significant. However, 58% are non-responders to the defined target sUr of 0.36 mmol/L (for 80% of the time during months 3 and 6), which is correlated with antibody formation to pegloticase and IRs. Moreover, 26%–31% of subjects experienced IRs and 77% suffered from gout flares (mostly in first 3 months). Although long-term data are awaited, an anti-immunologic or anti-inflammatory strategy is needed to prevent antipegloticase antibody formation, which is associated with IRs and diminished or shortened efficacy, and the strategy might also prevent gout flares induced by urate mobilization at the same time.

A good news for patients who cannot be treated with classic antihyperuricemic drugs is the recent availability of febuxostat and the development of other antihyperuricemic drugs that might be less efficacious than pegloticase but may well have a better benefit or risk balance in the long

term. Nevertheless, according to the current clinical data, pegloticase might have an important role as bridging treatment, eg, for 6 months in sUr responsive patients for rapid urate debulking in severe (treatment refractory) gout. After successful dissolution of tophi, a less rigorous regimen possibly with new drugs like febuxostat might be sufficient while maintaining a negative urate mass balance.

Pegloticase has been accepted for resubmission for approval by the FDA and may provide an important, novel option in patients with chronic refractory gout.

Disclosure

The authors have no conflict of interest to declare.

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