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Pegloticase in gout treatment – safety issues, latest evidence and clinical considerations

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***Abstract*:** Gout is a common rheumatic condition, with increasing prevalence in recent decades. The mainstay of treatment for gout is oral urate-lowering therapy (ULT), typically with xanthine oxidase inhibitors (XOIs). Unfortunately, a proportion of patients have persistent gout that is refractory to ULT. Pegloticase, a recombinant pegylated uricase, has been approved by the US Food and Drug Administration for the treatment of refractory gout. However, concern has been raised regarding the risk of infusion reactions, which are now understood to be largely due to the development of antipegloticase antibodies. Discontinuation of pegloticase upon failure to lower serum urate has been shown to markedly reduce infusion reaction risk, but deprives patients of what, in many cases, is a last-resort treatment. In this manuscript, we review the rationale, mechanism of action, efficacy and safety of pegloticase. Additionally, we focus on potential strategies to reduce pegloticase immunogenicity and potentially make this important agent available to a wider group of patients requiring treatment.

Keywords: gout, hyperuricemia, pegloticase, urate-lowering therapy

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Introduction

With increasing prevalence in the population,[1] gout has become a rising public health concern. As more people are affected, the number of patients with refractory gout, that is, disease that is unresponsive or inadequately responsive to conventional oral therapies, is believed to have increased as well.[2] For such patients, more effective and aggressive therapy is needed. Pegloticase (Krystexxa, Horizon Pharma; Dublin, Ireland), a recombinant pegylated uricase, was approved by the US Food and Drug Administration (FDA) in 2010 for chronic gout in adult patients refractory to conventional therapy (www.accessdata.fda.gov). In this manuscript, we review the efficacy and safety profile of pegloticase.

The burden of gout

Gout is characterized by the presence of hyperuricemia and the precipitation of monosodium urate (MSU) crystals, leading to clinical features of acute inflammatory arthritis, articular erosions, tophi, and in some instances, uric acid renal stones and nephropathy.[3–5] Increasing in concert with the aging population and the current epidemic of obesity and metabolic syndrome in the United States, gout is now the most common inflammatory arthritis, affecting at least 8.3 million (3.9%) US adults.[1,6] Of these, approximately 25,000–100,000 are estimated to be refractory to first-line treatment with oral urate-lowering therapy (ULT).[2]

Patients with severe gout and disease refractory to first-line agents pose a therapeutic challenge, and have thus become an area of focus in recent years. Though consensus definitions for these diagnoses are lacking, multiple classifications have been proposed.[7] According to some available definitions, severe gout is characterized by a large burden of MSU crystals with associated joint damage,

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and frequent or continuous flaring with multiple affected joints, associated comorbidities and possibly drug intolerance,[7] while refractory gout may refer to persistent arthritic symptoms, tophi or the inability to achieve serum urate (sUA) levels below the therapeutic target of 6.0 mg/dl, despite the use of conventional urate-lowering therapy.[4,8] As stated in the prescribing information for pegloticase, 'gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated [highlights of prescribing information, Krystexxa, https://hznp.azureedge.net/public/KRYSTEXXA_Prescribing_Information.pdf (accessed June 27, 2017)]. Several mechanisms may contribute to the development of both severe and refractory gout, including delayed prescribing, medication nonadherence with oral ULT, physician failure to titrate ULT doses to achieve target sUA concentrations, medication intolerance, or simply medication failure.[8] In many but not all cases, therefore, severe or refractory gout represents a failure of proper early screening and management, creating a difficult situation and a need for more aggressive therapy. Gout has been shown to have substantial impact on healthcare costs, functional disability and health-related quality of life,[9,10] and refractory gout contributes disproportionately to the overall burden of the disease.[2,8]

Gout treatment: lowering serum urate using standard therapies

As hyperuricemia and urate crystal deposition may persist and progress despite the suppression of inflammation, both American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) gout treatment guidelines recommend ULT for most patients.[6,11] The target sUA for most patients with gout is recommended to be <6.0 mg/dl (slightly below the solubility point of urate at 6.8 mg/dl); however, still lower target levels (e.g. <5.0 mg/dl or even lower) may be warranted for patients with more advanced or refractory disease.[11]

Xanthine oxidase inhibitors (XOIs) prevent the conversion of purines into uric acid, and are recommended as first-line urate-lowering therapies according to both ACR and EULAR guidelines.[6,11,12] Allopurinol is most commonly used given its wide availability and low cost. However, target sUA concentrations are not always achieved with allopurinol monotherapy, owing to medication nonadherence, inadequate dosing and titration, or medication failure.[12,13] Allopurinol also has a small but definite risk of severe cutaneous hypersensitivity reactions, particularly among patients of specific Asian backgrounds who are positive for the Human leukocyte antigen (HLA) B*5801 allele.[14,15] Febuxostat is a nonpurine, noncompetitive XOI, with less risk of hypersensitivity when compared with allopurinol.[15,16] Due to higher cost, febuxostat is often reserved for allopurinol contraindication, intolerance or ineffectiveness.[12]

Uricosurics, including probenecid and lesinurad (and benzbromarone in some European countries), increase renal uric acid excretion by inhibiting urate-reabsorbing transporters, particularly URAT1, in the proximal tubular cells of the kidneys.[12,17] Uricosurics are usually reserved for patients who cannot tolerate XOIs, or for combination use in patients with inadequate response to XOI monotherapy.[6] Probenecid is less commonly used due to dosing multiple times per day, drug interactions and relative ineffectiveness for patients with creatinine clearance less than 50 ml/min.[12,18] Lesinurad is easier to use, but is reserved exclusively for combination therapy with an XOI, as single-agent use conveys an increased risk for adverse renal effects, including an increase in serum creatinine.[12,17]

Despite the availability of multiple medications, a significant number of patients starting oral ULT fail to achieve adequate gout control,[8,19] owing to patient factors (e.g. patient comorbidities, inadequate understanding of their disease, inadequate compliance, refusal to accept treatment in the face of transiently increasing flares), physician factors (e.g. inadequate understanding of the disease, failure to treat to target, failure to support the patient through early treatment-related flares), and less commonly, true drug intolerance or inadequate drug effect, also described as 'partial resistance'.[13,20] One recent retrospective study showed that up to 69% of patients treated with oral ULT were inadequately controlled, defined as having sUA $>$ 6.0 mg/dl or more than two flares within the past 12 months. Additionally, oral ULT benefits may be delayed, with one survey showing less than one third of patients achieving complete disease control after 39 months of therapy.[21] Regarding tophaceous gout, oral ULT may dissolve tophi when target sUA concentrations are achieved,

however, the time to tophus resolution is prolonged [mean ± standard deviation (SD) of 20.8 ± 10.2 months] and typically requires combination therapy.[22] Given the considerable rates of inadequate response to treatment and extended time to tophus resolution with current therapies, the need for more effective urate-lowering treatment becomes apparent.

Uricase deficiency and uricase replacement: a different approach

The enzyme uricase metabolizes urate into the more soluble allantoin, which is readily excreted by the kidney.[19,23] While uricase is present in most mammalian species, the enzyme underwent mutational inactivation in humans and higher primates during the Miocene era (5–23 million years ago).[3,24] Theorists propose that the hominid loss of uricase may have been driven by an evolutionary advantage to maintaining higher levels of sUA.[24] Proposed advantages include antioxidant properties of urate that may have compensated for a prior genetic loss of the ability to synthesize ascorbic acid; urate acting to maintain blood pressure during an era of decreased salt ingestion (and hence, potentially, hypotension in upright mammals); benefits of higher levels of urate on alertness and intelligence; and a possible neuroprotective effect against neurodegenerative diseases.[24,25] Whatever benefits may have accrued, the loss of uricase resulted in a species-wide increase in baseline sUA levels that set the stage for some humans to experience additional rises in sUA above the molecule's saturation point.

The concept of using recombinant uricase to treat gout initially arose from a recombinant fungal urate oxidase, rasburicase, developed for children suffering from tumor lysis syndrome. Unfortunately, rasburicase's utility for gout is limited by its short half-life and immunogenic properties,[26] though one study comparing daily with monthly rasburicase infusions showed a potential benefit to monthly rasburicase in patients with severe gout.[27] In contrast, pegloticase is a mammalian recombinant uricase covalently conjugated to monomethoxypoly (ethylene glycol) in order to reduce immunogenicity and maximize solubility and serum half-life.[19,28] The mean half-life of pegloticase is approximately 2 weeks, significantly longer than its nonpegylated uricase counterpart.[23] Once administered intravenously, pegloticase remains in the circulation, where it degrades urate to allantoin, with the resulting urate concentration gradient drawing further extravascular urate into the circulation to be degraded by the recombinant enzyme. This ultimately leads to a marked decrease in the sUA concentration, relative resolution of tophi, and prevention of future gout flares.[19]

Pegloticase efficacy

Pegloticase was studied in replicate phase III double-blinded randomized placebo controlled trials (RCTs) enrolling 212 patients with refractory gout (defined as sUA $>$ 8 mg/dl, plus either: three or more flares in the previous 18 months; at least one tophus lesion; or chronic gouty arthropathy, despite allopurinol use or in the setting of allopurinol intolerance). Patients were randomized to receive pegloticase 8 mg every 2 weeks, pegloticase 8 mg every 4 weeks, or placebo for 6 months. The primary endpoint was a plasma uric acid (pUA) $<$ 6.0 mg/dl for 80% of the time, measured during months 3 and 6 of treatment. In these studies, a greater proportion of patients in both pegloticase treatment groups achieved the primary endpoint compared with placebo: 36/85 (42%) patients receiving every-2-week pegloticase, 29/84 (35%) patients receiving every-4-week pegloticase and 0/43 (0%) in the placebo group ($p < 0.001$). With regards to secondary endpoints, these studies also demonstrated a reduction in tophaceous burden with pegloticase (greater efficacy in the every-2-week treatment group), reductions in both tender joint count (TJC) and swollen joint count (SJC) in both pegloticase treatment groups compared with placebo (with reduction in TJC achieving statistical significance), and significant improvement in physical function and quality of life as measured by the Health Assessment Questionnaire (HAQ) pain scale, HAQ-Disability Index (HAQ-DI) and 36-Item Short Form Health Survey (SF-36).[19] The results from these trials resulted in the FDA approval of pegloticase (Krystexxa) in 2010.[19,29]

A 30-month open-label extension (OLE) study enrolling 96% of RCT completers assessed ongoing pegloticase efficacy in patients with tophaceous gout. During the OLE, all patients received pegloticase in either every 2 or every-4-week dosing intervals. Computer-assisted photographic evaluation in rheumatology (CAPER) methodology was used to assess tophus response during the RCT as well as during the OLE. By the end of the RCT, 40% of patients treated with pegloticase every 2 weeks attained an overall tophus complete

response (CR) compared with 7% in the RCT placebo group, with an even greater improvement achieved in pegloticase responders who achieved sustained pUA < 6.0 mg/dl. Furthermore, the proportion of patients with overall tophus CR increased with treatment length during the OLE, with 83% of pegloticase responders achieving overall tophus CR at the final OLE visit. This study highlights the efficacy of pegloticase on tophus resolution, with tophi resolving more rapidly than observed with oral ULT.[30]

Several smaller studies and case reports are available in support of the data obtained from the OLE. Araujo *et al.*[31] conducted a prospective observational study using dual-energy computed tomography (DECT) in 10 patients treated with pegloticase to evaluate tophus response, showing a 95% reduction in tophus volume in pegloticase responders (by clinical criteria), compared with a 48% reduction in nonresponders. A similar effect was observed in a report by Modjinou *et al.*,[32] in which a 32-year-old patient with chronic refractory tophaceous gout was found to have 100% resolution of three index tophi on DECT imaging within 6 months, despite the persistence of nonurate soft tissue lesions. Furthermore, a study by Dalbeth *et al.*[33] looking at serial radiographs in eight patients with tophaceous gout treated with pegloticase suggested that profound urate lowering with pegloticase may lead to improvements in bony erosions, as well as increased bone sclerosis, which may represent the restorative efforts of bone following crystal dissolution, a finding also observed in a case report by Berhanu *et al.*[34]

While the above studies have shown pegloticase to be effective in a subset of individuals, the question has arisen as to why certain patients respond extremely well to pegloticase therapy while others become partial or nonresponders. To address this question, Lipsky *et al.*[28] looked at the generation of antibodies to pegloticase in the patients enrolled in the phase III RCT, to determine whether immunogenicity might contribute to a loss of the urate-lowering response. In these analyses, patients in the every-2-week treatment group who were considered to be responders were shown to have rapid reductions in sUA, with levels persisting at <2 mg/dl throughout treatment. Patients deemed nonresponders also achieved a rapid transient reduction in sUA levels, but lost their urate-lowering response (urate levels rising to >6 mg/dl) soon after treatment initiation, with a mean time to loss of response (LOR) of 6 weeks. The distinguishing characteristic between responders and nonresponders was the development of antipegloticase antibodies in the nonresponder group, with nonresponder titers typically exceeding 1:2340. Perhaps surprisingly, the majority of the antibodies were directed toward the polyethylene glycol (PEG) moiety, which was initially engineered to reduce immunogenicity. These antibodies are likely to affect medication pharmacokinetics, increasing clearance and reducing drug concentrations to subtherapeutic levels, thus contributing to the LOR. A total of 41% patients receiving pegloticase developed clinically significant antipegloticase antibody titers with the capacity to affect drug levels, ultimately leading to elevated sUA concentrations, with mean antipegloticase antibodies rising to >1:2340 in nonresponders almost always by the week 4 visit (antibodies were assessed prior to visits, at weeks 3,5,9,13,17,21 and 25). These results suggest that the loss of a urate-lowering response as a consequence of developing antipegloticase antibodies occurs rapidly in most patients, and that patients who do not experience these events in the first few months of treatment are much less likely to experience them later on.[28]

Pegloticase intolerance: questions and answers

During the phase III trial and OLE, a number of pegloticase adverse reactions were identified. Adverse events (AE) occurred in up to 90% of patients receiving pegloticase during the 6-month RCT; by the end of the 30-month OLE in which all enrolled patients (n = 149) received pegloticase, 98% experienced at least one AE[19,35] (see Table 1 for the most common AEs identified in the compiled studies). The most common AE observed was gout flare, affecting 71% of patients during the OLE (despite flare prophylaxis with colchicine 0.6 mg once or twice daily, or nonsteroidal anti-inflammatory drugs initiated 1 week prior to the first infusion and continued throughout the study).[19] The highest flare rate occurred during the initial 3-month period of treatment, consistent with the understanding that gouty attacks occur during treatment initiation due to the rapid decrease in sUA and dispersion of MSU crystals into the tissues during MSU dissolution.[35] Clinical experience suggests that patients treated with pegloticase might be more susceptible to flares (either worse or more frequent) than patients treated with oral ULT, both because they tend to have severe disease, and as a result of

Table 1. Documented adverse events (AEs) with pegloticase in a phase III trial and open-label extension.

Adverse events	Range of reported AEs in a phase III trial and OLE
Gout flare	71–85%*
Infusion reactions: monthly pegloticase	42%
Infusion reactions: biweekly pegloticase	26%
Headache	9–11%*
Nausea	7–12%*
Back pain	4–17%*
Nasopharyngitis	5–10%*
Cardiovascular events: congestive heart failure, arrhythmia, unstable angina, deep venous thrombosis, transient ischemic attack, coronary revascularization	2–7%*
Cardiovascular death, nonfatal MI	1–2%*

Data obtained from trials by Sundy *et al.*[19] and Becker *et al.*[35]
Other observed adverse events: dyspnea, vomiting, chest pain, pyrexia, constipation, elevated blood pressure, peripheral edema, fatigue. Note that these numbers are inclusive of events adjudicated as both related and unrelated to pegloticase.
*Ranges compiled from both monthly and biweekly pegloticase infusion cohorts in a phase III and OLE.
OLE, open-label extension; MI, myocardial infarction.

the rapidity of serum urate-lowering and disruption of settled deposits that occurs with pegloticase. Such patients additionally may be more refractory to the prophylaxis standards, thus potentially requiring more aggressive flare prophylaxis regimens. Pascual *et al.*[7] propose regimens for both flare prophylaxis and management in these patients, including colchicine, low-dose NSAIDs or glucocorticoids, combinations of these therapeutic agents, and IL-1 inhibitors for patients who remain refractory. In the OLE, gout flares occurred less frequently in patients receiving pegloticase every 2 weeks who were considered to be pegloticase responders, compared with nonresponders, confirming that successful treatment eventually resulted in reduced flare rates. Although gout flares during pegloticase treatment may be taken as a mark of drug efficacy rather than an adverse response, they underline the need for appropriate and aggressive flare prophylaxis in this population of patients.

Infusion reactions (IRs) were the second most common AE observed, occurring in 26% of patients receiving every-2-week pegloticase and 42% of patients receiving every-4-week pegloticase during the RCT, and 44% of patients during the OLE study.[19,35] In part because of the increased intolerance in the every-4-week infusion group, pegloticase was ultimately approved for every-2-week administration only. The most common symptoms of IRs included musculoskeletal pain, flushing, erythema, nausea/vomiting, dyspnea, headache, changes in blood pressure and urticaria. Although a number of these events met rigorous FDA criteria for anaphylaxis, many were mild, and all IRs during the study resolved spontaneously without the need for intensive medical intervention.[35]

Other AEs observed during the studies included cardiovascular events, such as myocardial infarction, congestive heart failure and arrhythmia, occurring at similar rates in both pegloticase responders and nonresponders. Four deaths occurred during the OLE, three in the every-2-week, and one in the every-4-week pegloticase group. The time since the last pegloticase infusion ranged from 3–33 weeks, and the causes of death included anemia, secondary to myelodysplastic syndrome, pneumonia, sepsis, and multisystem organ failure. All four deaths were adjudicated to be unrelated to the study drug.[35]

Importantly, an increased rate of IRs was observed to be associated with the presence of elevated antipegloticase antibody titers. IRs occurred in 31/52 (60%) patients who developed antipegloticase titers $> 1{:}2340$, but in only 16/84 (19%) patients with titers $\leqslant 1{:}2340$ ($p < 0.001$). Unfortunately, the antibody titers at the time of the first reaction did not reliably predict the occurrence of an IR. On the other hand, the loss of urate-lowering efficacy, demonstrated by re-increase in sUA to >6.0 mg/dl after initial lowering, was observed in 91% of patients receiving every-2-week pegloticase, and 71% of patients receiving every-4-week pegloticase infusions who developed IRs.[19] Thus, the failure of urate lowering was found to be a surrogate for antipegloticase antibody presence that performed better as a predictor of IRs than the antibody titers themselves.

Based on these observations, a *post hoc* analysis of the RCTs assessed the impact of several guidelines for discontinuing pegloticase to minimize IRs. Using two consecutive sUA pre-infusion measurements > 6.0 mg/dl as an indication to discontinue pegloticase ('stopping rule') was shown to reduce the risk of IRs by nearly half (from 26% to 14%), with no adverse effect on the intention-to-treat response rate (42% *versus* 41%). Using a one-time measurement of sUA > 6.0 mg/dl as a guideline to stop pegloticase would have reduced the incidence of IRs to as low as 8%, but significantly fewer patients would have remained in the study to achieve the primary endpoint. Among patients able to maintain sUA < 6.0 mg/dl for the duration of treatment, the rate of IRs was as low as less than one event per every 100 infusions.[36] Based on these studies, current prescribing information recommends discontinuation of pegloticase in patients with two sequential sUA > 6.0 mg/dl (www.accessdata.fda.gov).

Though data in the postmarketing period is somewhat limited, one study looking at postmarketing AE reporting revealed IRs and anaphylaxis as the most common AEs (occurring in 20 and 8 patients, respectively). Additionally, this postmarketing study highlighted the potential risk of concomitant use of XOIs with pegloticase as they may mask loss of response, thus making the 'stopping rule' invalid.[37] However, more postmarketing data are warranted to ensure a comprehensive, long-term safety profile of pegloticase.

Potential strategies to minimize intolerance

While discontinuation of pegloticase in response to loss of efficacy markedly reduces the risk of IRs, pegloticase is reserved for patients with refractory disease, and cessation of therapy frequently leaves no adequate options for management of their recalcitrant gout. Thus, the question becomes, are there any ways to avoid the discontinuation of pegloticase due to LOR? Can pegloticase immunogenicity be reduced or abrogated altogether?

One possible approach to reducing immunogenicity is the use of immunosuppression to reduce the production of antidrug antibodies. Several reports suggest that immunosuppressive agents may improve pegloticase tolerance. Hershfield *et al.*[38] conducted an open-label, five-infusion trial in 29 patients with refractory gout receiving pegloticase, including 7 patients on immunosuppressant medications for prior organ transplantation (including mycophenolate mofetil, cyclosporine, azathioprine, and tacrolimus, in various dosages and combinations). In that study, only 1 of 7 (14%) organ transplant patients on immunosuppressive therapy developed antibodies to pegloticase, whereas 9 of 20 (45%) patients not receiving concurrent immunosuppressants developed antidrug antibodies. Thus, co-administration of immunosuppressants with pegloticase may preserve drug efficacy. Similar results were observed in a case reported by Berhanu *et al.*[34] in which a patient receiving treatment with both azathioprine and pegloticase experienced transient increases in sUA levels during two periods of azathioprine noncompliance, suggesting the possible unmasking of an immunologic response to pegloticase causing transient treatment failure that resolved with reinstatement of azathioprine. While these results are promising, prospective studies will be needed to determine whether immunosuppressants should routinely be given with pegloticase to decrease the rate of antidrug antibody formation with the aim of preserving drug efficacy.

An alternative, immunologic-based approach to pegloticase tolerance might be to prevent the initial development of pegloticase hypersensitivity. The previously mentioned studies show that a greater proportion of patients responded to pegloticase when it was dosed at every-2-week as compared with every-4-week intervals. Additionally, a greater proportion of patients developed IRs in the every-4-week treatment group compared with the every-2-week group, suggesting that the dosing interval may affect immunogenicity.[19,28] As proof of principle for this notion, one study in patients with inflammatory bowel disease receiving infliximab showed a positive effect of increasing the infliximab dose and decreasing the dosing interval to minimize the potential for immunogenicity.[39] Dosing intervals may be particularly important in the initial phases of administration, before the achievement of steady-state levels, when an extended dosing interval could potentially allow trough levels to fall low enough to allow activation of hypersensitivity mechanisms.[40] As a result, a phase II open-label nonrandomized study is currently underway to assess the effect of high-zone tolerance by more frequent early dosing at the initiation of pegloticase therapy (weekly infusions for the first 3 weeks of treatment) [ClinicalTrials.gov identifier: NCT02598596].

Oxidative stress

A theoretical concern with pegloticase is the potential for inducing oxidative stress.

In vitro studies have suggested that some level of urate may actually be protective in humans by scavenging free radicals, thus acting as one of the major antioxidants in human plasma. In contrast, pegloticase, in converting urate to allantoin, leads to the formation of hydrogen peroxide, thus providing a mechanism for oxidative stress induction. However, in examining the potential for a pegloticase-induced oxidant load to reach clinically concerning levels, Hershfeld *et al.*[25] demonstrated that erythrocyte membranes, which provide the major source of peroxidase to eliminate hydrogen peroxide in the plasma, have the ability to inactivate oxygen free radicals on the order of two to three times faster than they are generated by urate oxidation with pegloticase. These data render the oxidative stress hypothesis of pegloticase largely a theoretical concern in nearly all patients. However, pegloticase remains contraindicated for patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency who are at risk for hemolysis and methemaglobinemia in response to the pegloticase oxidant load, a side effect that had previously been observed with rasburicase, and which has been documented in case reports by Owens *et al.*[41] and Geraldino-Pardilla *et al.*[42] after pegloticase infusion.

How low is 'too low' for serum uric acid?

It has been well documented that elevated sUA, in addition to its association with gout and the resulting complications, is associated with increased cardiovascular and renal mortality.[43,44] However, as discussed previously, the uricase enzyme was selectively inactivated during human evolution, which is hypothesized to have acted advantageously during that era.[24] With the understanding that uric acid harbors some antioxidant properties, theories exist to suggest that urate may actually be protective and may positively impact survival. Most of the data regarding the survival benefits of urate relate to potential neuroprotective properties, with higher levels of sUA associated with improved outcomes in Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis (ALS). To date, no causal relationship has been elucidated,[25,45] but a phase III study is currently underway to evaluate whether pharmacologically induced elevations of sUA may be associated with reduced clinical progression of Parkinson's disease [ClinicalTrials.gov identifier: NCT02642393].

A recent study by Dahle *et al.*[46] identified a 'J-shaped' sUA curve for cardiovascular and all-cause mortality among patients who are postrenal transplant, with trends towards increased risk among patients with sUA levels < 3.49 mg/dl. However, these trends did not achieve statistical significance and were recognizable only in the subset of subjects who also had diabetes. Moreover, no attempt was made to identify risk effects specifically in patients with gout (who are likely to be at higher baseline cardiovascular risk than many other patients). Additionally, the long period of low urate exposure observed in these patients (median follow up 7.4 years) differs significantly from that in patients receiving pegloticase, who are typically treated for less than one year. Thus, the relevance of this study to gout patients receiving pegloticase remains uncertain at best.

Pegloticase in acute decompensated heart failure

Pegloticase has not been formally studied in patients with congestive heart failure (CHF). However in the phase III trials, two patients receiving every-2-week pegloticase, and one patient receiving every-4-week pegloticase developed CHF exacerbations. All of the affected patients had documented prior histories of cardiovascular disease. In the OLE, a total of four additional patients, all with prior diagnoses of CHF, experienced exacerbations of their heart failure while receiving pegloticase.[19,23,47] The mechanism(s) by which pegloticase might promote CHF exacerbations has not been characterized, but could potentially relate to volume overload during infusion in patients who are at a baseline increased risk. Thus, care should be exercised when treating chronic CHF patients with pegloticase, particularly those in a currently decompensated state.

Conclusions

Gout imposes a significant burden on our healthcare system, and an even more significant burden on the patients it affects. Although a number of oral urate-lowering medications have been developed to treat these patients, a significant degree of

treatment failure and refractory disease persists. Pegloticase was developed to treat refractory gout and has shown proven benefit in clinical trials and open-label extensions. However, pegloticase has the potential for inciting immunogenicity, and some patients develop antipegloticase antibodies with accompanying loss of efficacy and potential development of IRs. Discontinuation of pegloticase at the time of treatment failure dramatically decreases the potential for infusion reactions and renders the agent roughly as safe as other biologic infusions.

Unfortunately, since pegloticase is currently a 'last resort' medication, the consequences for patients who need to discontinue pegloticase therapy can be significant. Immunosuppression has shown potential for decreasing the rate of pegloticase failure, and high-zone tolerance approaches are also under active study. If effective, either of these strategies could be easily implemented in clinical practice, and would expand the spectrum of individuals who could benefit from pegloticase treatment.

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Dr Guttmann has nothing to disclose. Dr Berhanu serves as a site investigator for a trial sponsored by Bristol-Myers Squibb. Dr Pillinger reports that he is currently a consultant for Crealta/Horizon, AstraZeneca, Ironwood and SOBI, and currently serves as a site investigator for a trial sponsored by Takeda. Dr Pillinger is additionally supported in part by NYU CTSA grant 1UL1TR001445 from the National Center for the Advancement of Translational Science (NCATS), NIH. Dr Krasnokutsky has served as a consultant for Crealta/Horizon and Ironwood. Dr Krasnokutsky is supported in part by an Investigator Award from the Rheumatology Research Foundation, and was previously supported in part by a New York State Empire Clinical Research Investigator Program (ECRIP) award. This study is an independent work that has not been supported by any funding agency or any corporate sponsor. None of the corporate entities listed above played any role in manuscript design and preparation, or had any access to input to the manuscript prior to publication.

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