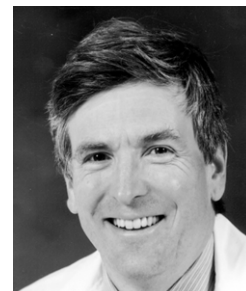# Learning How and When to Employ Uricase as Bridge Therapy in Refractory Gout

Clinicians are increasingly facing refractory cases of tophaceous gout in which a "perfect storm" of advanced age, comorbidities (e.g., diabetes and renal and heart failure), and drug interactions complicate management[1]. Debilitating polyarticular gout and anatomically destructive tophaceous disease become problematic when effective antihyperuricemic options are limited. The classic scenario is hypersensitivity or other significant intolerance to allopurinol with associated chronic renal insufficiency or uric acid overproduction. Potent, effective new antihyperuricemics are currently advancing in clinical development. These include the selective xanthine oxidase inhibitor febuxostat, which performed well in direct comparison with allopurinol in a phase III clinical trial[2]. Intravenous administration of uricase, an enzyme that has the therapeutically unique capacity to directly oxidize and thereby degrade uric acid, is another form of therapy in clinical development[3]. However, current unavailability of potent new antihyperuricemics necessitates consideration of "bridge therapies" for difficult cases to tide patients through periods of active, debilitating disease. This editorial assesses not only the potential immediate impact of Rasburicase[TM] as antihyperuricemic bridge therapy in gout (as tested by Richette, *et al* in this issue of *The Journal*[4]), but also emerging issues of how and when to employ uricase preparations in refractory disease.

RASBURICASE: AN INTERMEDIATE FORM IN THE THERAPEUTIC EVOLUTION OF URICASES

In nonprimate mammals and lower primates, uricase catalyzes the conversion of uric acid to allantoin, which is up to 10-fold more soluble and is readily excreted[3]. In evolution, production of the active uricase gene product has been mutationally silenced in higher primates and humans. Hence, uricase is not a physiologic enzyme replacement therapy, in contrast, for example, to administration of the modified glucocerebrosidase alglucerase in type I Gaucher's disease. Arguably, the primary benefit of uricase loss and consequent

5–6-fold higher physiologic serum urate levels in human evolution is limitation of oxidative stress and tissue damage[1]. Uric acid is our major circulating antioxidant. Moreover, slow, uricase-catalyzed conversion of uric acid to allantoin yields the oxidant hydrogen peroxide as a byproduct[1]. Neutralization by uric acid of the capacity of the potent and long-lived nitric oxide-derived oxidant peroxynitrite to induce neuronal and potentially other forms of major organ toxicity is a prime example of potentially beneficial antioxidant effect of uric acid[5,6]. Nevertheless, refractory tumor lysis syndrome and tophaceous gout are significant medical conditions that can therapeutically benefit from the unique capacities of uricase to directly and potently degrade soluble uric acid (and to dissolve directly contacted uric acid and monosodium urate crystals). Hence, multiple forms of uricase have been administered to humans (Table 1), as reviewed[7].

Nonrecombinant *Aspergillus flavus* uricase Uricozyme[TM] was first developed and applied in Europe in 1975 for prevention and management of tumor lysis syndrome[7]. Use of Uricozyme for hyperuricemia in gout associated with major organ transplants was described in the 1990s[7-9]. However, the extraction technology used to produce the enzyme was limited by low yield and cysteine modification. Frequent dosing was required due to short half-life, and potentially severe allergic reactions (including bronchospasm and anaphylaxis) occurred in up to 4.5% of subjects.

Recombinant *Aspergillus flavus* uricase (Rasburicase[TM]) replaced Uricozyme, and is currently approved by the US Food and Drug Administration (FDA) for short-term use in tumor lysis syndrome management in pediatric patients with malignancies[10]. Black-box warnings for Rasburicase notably include anaphylaxis but also complications of erythrocyte oxidative stress [hemolysis and methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency]. The incidence of severe acute hypersensitivity reactions is less with Rasburicase than

Uricozyme[10]. However, all forms of uricase are immunogenic in humans. Binding and neutralizing antibodies rapidly appear within weeks in the majority of subjects receiving Rasburicase. Moreover, the serum half-life of Rasburicase is less than 24 hours in pediatric subjects[10]. Hence, the most recent uricase clinical development efforts for refractory hyperuricemia of gout, where reduced antigenicity and longer half-life are needed for more sustained and effective therapy, have focused on modification of the tetrameric uricase enzyme by attachment of strands of polyethylene glycol (PEG)[3,7,11,12] (Table 1).

RASBURICASE AS "BRIDGE THERAPY" IN DIFFICULT GOUT

Lacking current approval by the FDA (or foreign equivalent) of any uricase for gout treatment, off-label use of Rasburicase is being explored for this indication when other available and potent antihyperuremic options are exhausted[13,14]. Richette, *et al* describe the largest to date of these pilot studies[4]. They retrospectively observed 10 subjects, all with chronic tophaceous gouty arthropathy and with mild to severe renal insufficiency, and all with allopurinol previously discontinued because of cutaneous hypersensitivity in 5 patients that was severe (Richette, personal communication), or allopurinol-refractory hyperuricemia in the other 5. All subjects, with appropriate informed consent, received infusions of Rasburicase 0.2 mg/kg intravenously over 30 minutes, with intravenous methylprednisolone (60 mg) as premedication[4]. In 5 subjects, a single, short, intensive management regimen of 5 daily infusions (adapted from regimens used for tumor lysis syndrome) was associated with profound acute lowering of serum urate but lack of sustained antihyperuricemic effects by 1 month, and lack of gross

tophus "de-bulking." The other 5 subjects received an empiric regimen of 6 monthly Rasburicase infusions, with more effective and sustained mean serum urate-lowering (from ~10 mg/dl to ~5.6 mg/dl after the sixth of the monthly infusions). There was gross evidence of "tophus de-bulking" in 2 such subjects[4]. The less than 24-hour serum half-life of uricase theoretically renders a relatively small fraction of total free urate stores accessible to Rasburicase in serum in patients with typical chronic tophaceous gout. Therefore, one suspects that the monthly regimen induced substantial serum urate-lowering by 6 months because Rasburicase was entering, dwelling, and acting at sites of peripheral tissue urate accumulation.

The study of Richette, *et al* suggests late problems due to immunogenicity when receiving monthly Rasburicase infusion in gout. One patient each developed bronchospasm or urticaria at the sixth infusion[4]. Longer-term, cutaneous allergic reactions necessitated Rasburicase discontinuation within 8 months in 2 other study patients receiving monthly treatment; while after 14 infusions, one patient's hyperuricemia became refractory to Rasburicase, and a new tophus appeared (presumably reflecting effects of neutralizing antibodies) (Richette, personal communication).

RASBURICASE AND GOUT FLARES: "NO PAIN, NO GAIN"

Despite adjunctive methylprednisolone use, gout flares, a classic event early in intensive uric acid-lowering treatment[1-3], were very common and could be difficult to control in patients receiving Rasburicase[4]. However, only one patient of the 6 with gout flares was reported to withdraw in the study of Richette, *et al*[4]. It is not yet clear whether profound serum-lowering by uricase, or possible direct uricase

Table 1. Uricases studied in humans to date. Therapeutic evolution of uricases is described in greater detail in the text.

Name	Preparation Methodology	Species of Origin	Status
Hog liver uricase	Nonrecombinant	Pig	No longer in clinical development
Uricozyme[TM]	Nonrecombinant, purified from fungal cultures	*Aspergillus flavus*	No longer manufactured
Rasburicase[TM], Fasturtec[TM], Elitek[TM]	Non-PEGylated, produced by a genetically modified *Saccharomyces cerevisiae* strain	Uricase cDNA from *Aspergillus flavus*	FDA-approved for management of tumor lysis syndrome in pediatric malignancies
Uricase-PEG5	Nonrecombinant, PEGylated (5 kDa PEG strands)	Uricase cDNA from *Candida utilis*	No longer in clinical development
Uricase-PEG5	Nonrecombinant, PEGylated (5 kDa PEG strands)	Uricase cDNA from *Arthrobacter protofomiae*	No longer in clinical development
Uricase-PEG 20[TM]	Recombinant, PEGylated (20 kDa PEG strands linked via succinimidyl succinimide	Uricase cDNA from *Candida utilis*	Phase I studies
Puricase[TM], PEG-Uricase	Recombinant, PEGylated (10 kDa covalently attached PEG strands)	Mammalian cDNA (mainly porcine, with baboon C-terminal sequence)	In Phase III trials

accessibility to tophaceous urate deposits, could affect inflammatory potential of crystals from remodeling tophi and thereby render gout flares different than those with standard antihyperuricemic therapy. Nevertheless, clinicians should be able to tide patients through early gouty arthritis flares with combinations of analgesics and corticosteroids and other antiinflammatories in order to achieve expedited benefits of possible tophus resolution within months via the most dose-intensive uricase "induction regimens." In doing so, it will be intriguing to assess in a randomized and controlled manner if interleukin 1ß inhibition (e.g., as described in a pilot study with anakinra[15]) or caspase-1 inhibition[16] can provide an effective alternative as primary antiinflammatory "bridge therapy" or build a "bridge therapy within uricase bridge therapy."

WEIGHING CLINICAL VALUE OF RASBURICASE RELATIVE TO PEGYLATED URICASES IN GOUT

With the described monthly Rasburicase regimen, an issue that looms larger than precipitation of early gout flares is the unimpressive overall performance when cost and risk of serious side effects are weighed against likelihood of meaningful clinical benefits. A more intense "induction regimen" (e.g., using Rasburicase 0.15 mg/kg intravenously every 2 weeks for several months)[13] would likely achieve more satisfactory serum urate levels and tophus size reduction[13]. However, prolonged Rasburicase regimens appear limited by immunogenicity related side effects and difficult to sustain for more than 6–15 months[4]. The longer serum half-life and reduced (although not abrogated) antigenicity achievable by uricase PEGylation[3,7,11,12] portends that intravenous PEGylated uricase can achieve both tolerance and performance substantially superior to Rasburicase for urate-lowering bridge therapy in refractory gout.

SUMMARY AND DRAFT GUIDELINES FOR INITIATING URICASE BRIDGE THERAPY IN REFRACTORY GOUT

Uricase infusion is an intense form of therapy with a cell-derived agent, essentially representing a biologic for gout and best employed for this indication by practitioners with appropriate training and experience. The use of uricase for gout mandates thorough consideration of pretreatment and posttreatment alternatives and complementary therapeutic modalities. Consensus guidelines for initiation, modes, and duration of uricase as bridge therapy in refractory gout would assist clinicians. Draft guidelines for uricase therapy in gout proposed here in Table 2 emphasize definition of the allopurinol treatment failure that so often is the crux of refractoriness. For mild allopurinol cutaneous hypersensitivity, oral allopurinol desensitization can be attempted, but is cumbersome, has a high failure rate, and can burn months of the most valuable bridge therapy time in refractory gout patients[17]. There is little debate about severe cutaneous

hypersensitivity representing allopurinol treatment failure, as in Richette, *et al*[4]. However, daily renal function-adjusted doses of allopurinol of 50 mg in one subject, 100 mg in 2 subjects, 200 mg in one subject, and 300 mg in one subject (Richette, personal communication) in the Rasburicase pilot study[4] appeared low overall. Standard management of allopurinol-tolerant patients with refractory, tophaceous gout due to persistent hyperuricemia includes slow, but steady and carefully monitored increases in allopurinol maintenance doses substantially beyond the appropriately renal function-adjusted allopurinol starting doses[18]. Because of clinical pharmacologic limitations of allopurinol, such a strategy will not work quickly, or may fail entirely in many with refractory gout, yet it is generally applicable and the risk of precipitating major allopurinol hypersensitivity syndrome is low[18].

The clinical performance of Rasburicase in gout appears uneven and difficult to sustain[4,13,14]. However, uricases have the potential to induce the melting away of tophi within months[3,4,13,19]. At present, the longer-term tolerability, safety, and cost-effectiveness of uricases remain to be defined in gout patients. Hence, the current primary indication for uricases in gout management remains limited-term antihyperuricemic bridge therapy in carefully selected patients with bona fide failure of oral antihyperuricemic treatment.

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Table 2. Draft guidelines for using a uricase as bridge therapy in refractory gout. Guidelines for disease modifying therapeutics in rheumatic diseases meld evidence-based clinical experience with consensus opinion in an effort to assist rheumatologists with appropriate treatment decisions and strategies. These draft guidelines are based on personal opinion rather than evidence, but are also rooted in evidence-based gout management[18]. Such guidelines are subject to regular revision to stay current with emerging data on appropriate ways to use uricase in gout, ways to employ other novel antihyperuricemics and novel and more effective antiinflammatory strategies for gouty arthritis, and their validated outcomes.

A. Prerequisites for uricase treatment in gout:

1. Meet American College of Rheumatology criteria for the diagnosis of gout

2. Have frequent acute gouty arthritis flares, and/or chronic polyarticular gout, and/or tophi

3. Have hyperuricemia and have failed standard oral antihyperuricemic drug therapy, as defined by failure to respond to or inability to tolerate an adequate therapeutic trial of allopurinol, and additional failure to respond to uricosuric therapy or the a priori inability of uricosuric therapy to satisfactorily and safely lower serum urate levels due to renal impairment or uric acid overproduction. Adequate therapeutic trial is defined as:

(a) Treatment for > 6 months, with at least 2 months at an appropriate dose, which for allopurinol is recommended to be a maximum target dose several-fold beyond the renal function-adjusted starting dose[18], unless significant side effects have limited the dose tolerated.

(b) Treatment for < 6 months, in which case treatment was stopped due to drug intolerance or toxicity, or treatment failed to control particularly active tophaceous joint and connective tissue destruction (e.g., by large, open, draining tophi).

B. Exclusion criteria. Although reference should be made to drug data sheets for individual uricases, the primary exclusions are:

1. G6PD deficiency

2. Congenital or idiopathic methemoglobinemia. Uricase should be used with caution in those receiving treatment with methemoglobin-inducing agents (see below)

3. Prior history of hypersensitivity to uricase

4. Women who are pregnant or breastfeeding

C. Criteria for withdrawal of therapy

1. Development of hemolysis or methemoglobinemia, or significant uricase-related hypersensitivity or organ toxicity

2. Lack of, or the loss of adequate antihyperuricemic response. Neutralizing antibodies that inhibit uricase therapeutic efficacy may develop during therapy. The potential for dosing adjustments of uricase preparations to overcome therapeutic limitations imposed by the development of neutralizing antibodies is not yet established. The effects of prior administration of one uricase on antibody development that influences effectiveness (and tolerability) of another uricase preparation are not yet known. Please see Section D.5 below regarding potentially misleading measurements of serum urate due to uricase presence in serum

3. Pregnancy or selected severe intercurrent illness (temporary withdrawal)

D. Potential adverse effects related to uricase therapy and guidelines related to these events:

1. *Anaphylaxis.* Uricase therapy should be discontinued immediately and permanently if anaphylaxis is triggered by drug infusion.

2. *Urticaria, bronchospasm, and other infusion reactions related to drug hypersensitivity.* Uricase therapy should be discontinued immediately and permanently if a serious hypersensitivity reaction is triggered by drug infusion. It is not yet defined if premedication with corticosteroids or antihistamines significantly reduces drug hypersensitivity and infusion reactions with uricase. Studies to address cross-sensitization between uricases and effects of prior administration of one uricase on tolerability of another have not yet been done.

3. *Hemolysis or methemoglobinemia.* G6PD screening should be conducted before initial uricase administration, with those of African and Mediterranean ancestry recognized to be at greatest risk. The hemogram should be monitored regularly with uricase therapy and cyanosis assessed for during infusion. G6PD deficiency is recognized to predispose to uricase-induced methemoglobinemia, but caution also should be exercised in patients taking drugs associated with methemoglobinemia, such as acetaminophen, benzocaine, dapsone, hydroxychloroquine, nitrofurantoin, nitroglycerin, nitroprusside, phenobarbitol, phenytoin, primaquine, and quinine.

4. *Flares of gouty arthritis.* Flares of gouty inflammation do not constitute an indication to discontinue uricase therapy and should be managed with standard antiinflammatory regimens used for gout[18]. It is not yet defined if adjunctive corticosteroid therapy with uricase infusions, or daily low-dose prednisone, reduce uricase-associated gout flares or whether biologic antiinflammatory treatment via IL-1ß antagonism is effective in this setting.

5. *Inaccurate measurement of serum urate due to uricase presence in serum.* Blood must be collected into prechilled heparinized tubes and assayed at 4˚C within 4 hours of collection.

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