

Treatment Failure Gout

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Treatment options for gout are well established and reasonably effective.¹ They include anti-inflammatory agents such as **non-steroidal anti-inflammatory drugs (NSAIDS)**, glucocorticoids and colchicine and urate-lowering therapies such as allopurinol and probenecid. However, despite the availability of effective urate-lowering therapy, there remains a subset of patients with gout who, despite aggressive therapy, have intractable disease, manifest as recurrent gout flares, chronic arthritis and progressive tophaceous deposits. These patients are referred to as having "refractory gout" or "treatment failure gout" (TFG).¹ The term "treatment failure gout" includes five ways by which patients may develop poorly controlled disease. These pertain mainly to the use of urate-lowering therapy and include delayed prescribing, inadequate dosage, intolerance, noncompliance and inadequate response in spite of generally acceptable dosages.² (Table 1) The new xanthine oxidase inhibitor febuxostat (Uloric) has not been studied in TFG, but may ultimately prove useful for this indication. Febuxostat is discussed elsewhere in this journal.

Regardless of the pathway, all patients with treatment failure gout are unable to reduce and maintain serum urate below the therapeutic target of 6 mg/dl.² An estimated 100,000 to 300,000 of the nearly 3 million cases of gout in the US are not adequately managed with current therapies.³ Additionally, many patients with gout have significant and multiple co-morbidities that preclude the use of those therapies.

Allopurinol, the most common treatment used to lower serum urate levels, is generally regarded as safe and effective.³ It lowers serum urate by inhibiting the purine nucleotide pathway enzyme xanthine oxidase. However, about 20% of patients receiving allopurinol report side effects and about 5% discontinue the medication due to intolerance.⁴ Allopurinol may also be contraindicated because of potential adverse drug interaction with azathioprine.⁵ Moreover, the presence of kidney disease may preclude ad-

equate dosing because allopurinol-related toxicity is increased in the presence of significant renal impairment. Even though severe toxicity is rare, inadequate dosing of allopurinol to achieve target serum urate level <6.0 mg/dl is common. Non-compliance is another common problem with allopurinol: in one study patients in a managed care cohort were non-compliant with allopurinol about 44% of the time.²

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Probenecid is the only uricosuric agent available in the United States. However, its use has declined due to important interactions with several other medications such as heparin, furosemide, aspirin and NSAIDS. Dosing is also a problem since probenecid is optimally administered twice or thrice daily, making full compliance difficult. There is also risk of central nervous system toxicity manifesting as seizures and respiratory arrest at higher doses.^{4,5} Most importantly, probenecid loses all of its uricosuric activity when the glomerular filtration rate falls below 50 ml/minute, a common situation in patients with gout.³

Benzbromarone is a more potent uricosuric agent than probenecid. It is effective even in patients with moderate renal failure. However, it is potentially hepatotoxic, with reports of fatal hepatitis, and is not commercially available in the United States.^{4,6}

Additionally, the use of uricosuric agents requires that patients maintain adequate hydration because the risk of nephrolithiasis is increased in poorly hydrated patients, particularly individuals

with cardiovascular disease or those receiving diuretic agents.

Patients with TFG experience significant joint pain and swelling, impaired functional status, chronic pain and reduced quality of life. In a recent study to assess the quality of life and disability in a group of subjects with TFG, the authors found that severe gout is associated with poor health related quality of life (HRQOL) and disability, especially for patients who experience more gout flares and have greater number of joints involved.⁷

Accordingly there is a need for improved therapies that will allow treatment for this population by controlling the consequences of hyperuricemia. Fortunately, several newer agents developed or being developed will be useful for patients with TFG. We will review pharmacologic therapy and also address the role of surgery in patients with TFG.

URICASE

"Urate oxidase" or "uricase" is a hepatic enzyme that catalyses the enzymatic oxidation of uric acid to allantoin, a more soluble and easily excreted end product of purine metabolism.⁴ Humans and higher primates experienced the mutational loss of the enzyme uricase during the process of evolution. The absence of a functional urate oxidase gene predisposes humans to hyperuricemia and gout.²

In contrast to allopurinol, which prevents the production of uric acid, uricase is capable of reducing existing urate stores such as found in gouty joints and tophi. Thus treatment with uricase has potential as a powerful therapy for the management of severe tophaceous gout.⁴

Two types of uricase, rasburicase and pegloticase, have been studied for the treatment of gout.

RASBURICASE

A purified fungal (*Aspergillus flavus*) uricase has been used for many years in Europe to prevent urate nephropathy during chemotherapy for hematologic

Table 1. Mechanisms of Treatment Failure Gout

1. Physician failure to diagnose and treat gout
2. Inadequate dosing of urate-lowering therapy
3. Allergy or intolerance to urate-lowering therapy
4. Inadequate response to adequate dosing of urate-lowering therapy
5. Lack of compliance with prescribed therapy

malignancies. A recombinant *Aspergillus flavus* uricase, known as rasburicase, became available in the US in 2002 and has been approved by the Food and Drug Administration (FDA) for use in patients for the prevention of tumor lysis syndrome after chemotherapy.^{8,9} For this indication, the recommended dosage is 0.20 mg/kg per day for 5-7 days administered **intravenously (IV)**. It has been demonstrated to be superior to allopurinol in the control of serum urate in a randomized trial of pediatric and adult patients at risk for tumor lysis syndrome.¹⁰ Although the FDA has not approved rasburicase for the management of gout, a number of case reports and small series have described its use in patients with severe tophaceous gout.

A 56-year-old woman with chronic renal insufficiency and severe recurrent gouty arthritis who had an allopurinol hypersensitivity reaction was treated successfully with 10 IV infusions of rasburicase over 16 months. Rasburicase treatment was well tolerated without allergic side effects, but she did have gout flares during the first three infusions. After the sixth infusion, the patient had dramatic regression of hand synovitis, resolution of gouty tophi and restoration of functional capacity to both hands. Her renal function remained stable.¹¹

Another case was reported of a 33-year-old renal transplant patient with recurrent gout attacks and an allergy to allopurinol. She had also had surgery for recurrent tophi. She was begun on rasburicase infusions at a dose of 0.15 mg/kg IV monthly. Rasburicase therapy was well tolerated and produced no adverse effects other than occasional gout flares which resolved with a decrease in the dose. During the 3 years of treatment the patient experienced resolution of gout attacks; the size of tophi decreased substantially and her functional status improved.¹²

In a retrospective study of 10 pa-

tients, the short term safety and efficacy of rasburicase 0.2 mg/kg in monthly vs. daily dosing schedules was compared in patients with renal failure and tophaceous gout, not adequately treated by allopurinol. The 5 patients receiving a daily infusion for 5 days had rapid but not sustained reduction in serum urate concentration and did not have any reduction in tophus size. Fifty percent of the patients in the group receiving monthly infusions for 6 months had reduction in tophus size. Serum urate was dramatically decreased with maximal decline at 7 days. Eight of ten patients experienced gout flares that were treated with colchicine and NSAIDs. Two patients also had hypersensitivity reactions to the medication.¹³

Rasburicase has a short half-life (18 hours) requiring repeated infusions. It is known to be antigenic. This raises the concern for hypersensitivity and decreased efficacy with repeated administration. Studies have demonstrated that time to detection of antibodies ranges from 1-6 weeks after administration and that the presence of antibodies is not associated with severe side effects. One of the byproducts of urate breakdown by uricase is hydrogen peroxide. Therefore G6PD deficiency contraindicates treatment with rasburicase because of risk of hemolysis. Other side effects include fever, respiratory distress, sepsis, neutropenia and mucositis.¹⁴

Although the results from these reports appear promising, data regarding optimal dosing and interval between infusions are lacking due to the absence of larger clinical studies of rasburicase in gout.

PEGLOTICASE

Pegloticase is a genetically engineered, recombinant polyethylene glycol (PEG)-conjugated mammalian uricase. A pegylated form of uricase has been formulated with the potential for reduced

immunogenicity and a longer half-life. Pegloticase has been studied extensively to evaluate both efficacy and safety in treatment failure gout. It is undergoing clinical trials in human subjects.

The results of two phase I clinical trials involving subcutaneous and IV infusions of PEG-conjugated uricase (pegloticase) demonstrated that this agent rapidly lowered and maintained serum urate levels at <6.0 mg/dl for a 2-3 week period. The bioavailability, efficacy and tolerability of IV pegloticase were greater than that of subcutaneous pegloticase.^{15,16}

In a phase II trial, 41 patients were randomized to undergo 12 weeks of treatment with IV pegloticase at 4 or 8 mg every 2 weeks for six doses, and 8 or 12 mg every 4 weeks for three doses. Serum uricase activity, serum urate and anti pegloticase antibodies were measured. Pegloticase was effective in rapidly reducing and maintaining serum urate levels at <6mg/dl in most patients in whom conventional therapy had been unsuccessful. The most effective dose was 8 mg every 2 weeks. The most common side effects were gout flares, which were mild to moderate in severity.¹⁷

The results of phase III clinical trials were presented in abstract form at the American College of Rheumatology meeting in 2008. Two hundred twelve patients with TFG were treated with IV pegloticase or placebo in replicate 6 month randomized, double blind studies. Subjects were randomized to pegloticase 8 mg q2week, 8mg q4week or placebo. The primary endpoint was plasma uric acid concentration <6mg/dl and the secondary endpoints were reduction in tophus size, gout flare incidence, swollen joints, tender joints, quality of life by SF-36 and disability by HAQ-DI and safety. Complete resolution of =1 tophus occurred in 21/52 q2week, 11/52 q4week and 2/29 placebo subjects. SF-36 physical component summary score and HAQ-DI for physical functioning improved significantly in both groups.

Gout flares and infusion reactions were the most common adverse events. Infusion reactions were the most common reason for withdrawal. The study concluded that 40% of patients treated with pegloticase achieved primary endpoint.

SURGICAL THERAPY FOR GOUT

The use of surgical intervention for gout dates back to the time of Hippocrates, when relief from severe pain was provided by burning the painful tophus with crude flax. Before the introduction of effective urate lowering therapy in the management of gout, surgery was frequently used for cosmetic reasons or for removal of large deposits of sodium urate.¹⁸

Tophi are characteristically deposited in articular and periarticular structures, and have a predilection for avascular structures. Nerves, blood vessels and muscles are not usually involved. Straub et al condensed and reclassified the earlier indications of Linton and Talbot for surgery in gout into four main categories: 1) functional: excision to permit wearing of shoes and clothing, restoration of motion, and stabilization of joints; 2) symptomatic: control of drainage and infection, reduction of pain and decompression of nerves; 3) cosmetic restoration and 4) metabolic: decrease of total body urate.¹⁹

The role of surgery for gout is now generally limited to the complications of tophaceous disease which include infection, nerve compression due to mass effect of the tophus, joint deformity and intractable pain. Tophaceous gout may compress peripheral nerves, the cauda equina or the spinal cord in which case prompt surgical intervention is needed to prevent permanent neurological impairment.

In a retrospective analysis of 45 patients who underwent surgery for gouty tophi, sepsis control in infected or ulcerated tophi was the main indication for surgery (51%), followed by mechanical problems caused by foot, elbow and hand tophi (27%). Four percent of patients underwent tophus surgery mainly for pain control.²⁰

Recurrence of tophi is unpredictable. In the series of Straub, 36 procedures were performed and tophi recurred in only 3 cases. However, few clinical trials address the long term efficacy of surgery in the management of tophaceous disease.

It is universally recommended that before surgery is considered for the treatment of gout, optimal urate-lowering medical therapy should be employed to reduce the size of tophi.

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Discussion of off-label usage of product: pegloticase, rasburicase

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