New Biological Agents for the Management of Refractory Gout

Learning Objectives
After participating in this educational activity, participants should be better able to

1. Monitor serum uric acid in order to set and achieve the target levels using all modes of therapies
2. Anticipate and manage adverse events associated with aggressive urate-lowering therapy (ULT)
Overview of Refractory Gout

With the overall prevalence of gout on the rise and the severity of this disease increasing in many patients, there has been a corresponding rise in the number of patients who are refractory to traditional treatment strategies for gout. Refractory gout refers to patients with persistent gout symptoms such as visible tophi and acute flares of gouty arthritis, and in whom serum uric acid (SUA) concentrations remain stubbornly above 6.8 mg/dL. It is a painful and debilitating condition, and one that affects approximately 30,000 patients in the United States.

There are multiple factors that may lead a patient to become refractory to treatment, including allopurinol intolerance, insufficient escalation of allopurinol, inadequate prophylaxis, multiple comorbidities, lack of follow-up, and poor patient adherence to therapy.[1] The two main pathways to refractory condition are 1) intolerance of conventional therapies, and 2) poor control with conventional therapies. Sensitivity to allopurinol, the first-line drug conventional therapy, is most often associated with side effects ranging from pruritic rash, cutaneous reaction, and/or gastrointestinal symptoms.[2-4] Intolerance to allopurinol can be overcome by switching to febuxostat, another xanthine oxidase inhibitor, or by switching to the off-label combination of allopurinol or febuxostat with probenecid.[5] In cases of poor control with conventional therapies, the pathway to a refractory state is often related to inadequate allopurinol escalation and poor patient adherence to therapy.[1]

Unfortunately, many patients fail to respond to traditional therapies for gout. In the past, there was little alternative for clinicians who care for refractory patients. This changed in September 2010 when the U.S. Food and Drug Administration (FDA) approved pegloticase (8 mg/dL IV q2 weeks) for the treatment of refractory gout.[6] We explore its safety and efficacy in the next section using two patient cases illustrating evidence-based and guideline-based treatment.
Strategies for Treating Gout

Table 1. Strategies for Lowering Serum Uric Acid in Gout Patients

<table>
<thead>
<tr>
<th>Pharmacologic Approach</th>
<th>Method of Action</th>
<th>Adverse Effects, Limitation, and Contraindications</th>
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</thead>
<tbody>
<tr>
<td><strong>Uricostatic Agent</strong></td>
<td></td>
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<tr>
<td>Allopurinol</td>
<td>Suppress uric acid formation</td>
<td>Dermatologic reactions, GI effects, severe hypersensitivity</td>
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<tr>
<td><strong>Uricostatic Agent</strong></td>
<td></td>
<td></td>
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<tr>
<td>Febuxostat</td>
<td>Suppress uric acid formation</td>
<td>Abnormal LFTs, nausea, arthralgia, rash</td>
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<td><strong>Uricosuric Agents</strong></td>
<td></td>
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<tr>
<td>(eg, probenecid)</td>
<td>Renal uric acid elimination</td>
<td>Dermatologic reactions, GI effects, renal calculi, contraindicated in patients with uric acid overproduction</td>
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<tr>
<td><strong>Uricolytic Agents</strong></td>
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<tr>
<td>(“Biologic”) uricases (eg, pegloticase)</td>
<td>Converts urate to more soluble allantoin</td>
<td>Intravenous infusion may be impractical; immunogenicity is common; adverse effects include high risk of infusion reactions, including anaphylaxis, and frequent gout flares</td>
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Treating Gout With Urate-Lowering Therapy

Traditional first-line therapies for gout patients include the urate-lowering strategies outlined in Table 1. It is important for primary care clinicians to note that, as stated in the previous section, the pathway to a refractory state is often attributable to inadequate escalation of allopurinol.[1] Among gout patients, 97% of prescriptions are for 300 mg or less of allopurinol, despite a maximum recommended daily dose of 800 mg.

Effective gout management in the primary care setting includes the titration of allopurinol since 300 mg a day is effective in less than half of patients.[1] Initial doses may be 100 or 150 mg per day, and SUA level should be assessed at two weeks post initiation of ULT. If the value is greater than 6.0 mg/dL, increase the dose by 100 or 150 mg. The uric acid level should be checked again after two weeks. This process should be repeated until the lowest dose that reduces the uric acid level to less than 6.0 mg/dL is determined.

It is important to note that while the recommended SUA target is 6.0 mg/dL for gout patients, it may be necessary and beneficial to target an even lower concentration in some patients, particularly those who are refractory to treatment. Maintaining the SUA at any level less than 6.8 mg/dL will eventually eliminate all the deposited uric acid from the body. However, the lower the SUA, the faster the uric acid will be cleared. Because refractory gout is disabling, it is recommended that the SUA be brought below 4.0 mg/dL to more rapidly clear the crystals.[7]
Treating Acute Gout Flares

Treatment of acute flares is another critical component of gout management, particularly in patients who are refractory to treatment. The choice of agents to use is among NSAIDs, colchicine, and corticosteroids.[8-10] The agent selected should be based on the patient’s comorbidities. For example, a patient with chronic kidney disease, hypertension, diabetes, or congestive heart failure should not take an NSAID. Colchicine is not advised in patients with poor renal function.[11] Regardless of the agent selected, it is essential that patients realize that they must take the medication at the very first hint of a gout flare. If they take the medication soon enough they may be able to abort the attack. If they wait too long, they may have to take medication for days. In addition, since each agent works by a different mechanism, they can be used in combination for severe flares.

Prophylaxis

Achieving optimal outcomes for patients with refractory gout requires that keen attention be paid to prophylaxis, particularly when initiating new therapies. Although it may seem paradoxical, gout flares often occur when initiating ULT. In fact, the lower and faster the serum uric acid drops, the more likely there is to be a flare.[12,13] Using low-dose colchicine or NSAID, beginning two weeks prior to starting the ULT, can significantly decrease this flare rate.[12,13] Once started, prophylaxis should be continued for approximately six months, although this interval may have to be extended in those with chronic tophaceous gout.

Evidence for Biologics for Refractory Gout

Patients with refractory gout often face a life of disability and considerable pain. Effective strategies are needed to control urate crystal deposition in the joints and to minimize tissue damage and loss of function. Biologics can achieve this goal.

Figure 1. Action of Uricase on Uric Acid

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\text{URIC ACID (relatively insoluble)} + 2 \text{H}_2\text{O} + \text{O}_2 \rightarrow \text{URICASE} \\
\rightarrow \text{ALLANTOIN (relatively soluble)} + \text{CO}_2 + \text{H}_2\text{O}_2
\]
Uricase, which catalyzes the conversion of uric acid to allantoin, is the enzyme present in other animals, which prevents them from accumulating uric acid and developing gout. Uricase holds promise as a strategy for managing SUA levels in patients with refractory gout. Previously, a fungal uricase preparation, rasburicase, was approved for the use in patients with tumor lysis syndrome. This agent dramatically lowers SUA but proved to be too antigenic to be used on a repeat basis, as would be needed to treat hyperuricemia in patients with gout.[14]

Pegloticase, a monomethoxypoly (ethylene glycol)-conjugated mammalian recombinant uricase, was FDA-approved in 2010 for the treatment of refractory gout. This agent also dramatically lowers SUA and has been used successfully over longer periods of time.[15,16] Although infusion reactions and anaphylaxis were encountered in clinical trials, it was learned that these occur only after the patients had developed blocking antibodies.[15] Therefore, pegloticase can be used safely as long as it is causing a reduction in SUA levels. If, however, the SUA is not less than 6.0 mg/dL two weeks after the last infusion, then antibodies have formed and the biologic should be discontinued.

**Pegloticase in Clinical Trials**

The first of the clinical trials was a three-month, open-label randomized controlled study on patients with refractory gout that compared efficacy and tolerability of pegloticase with placebo in lowering uric acid and clinical outcomes. The second study looked at the efficacy of pegloticase for refractory gout patients in a six-month treatment regimen in two replicate, randomized, double-blind, and placebo-controlled trial from June 2006 to October 2007 (n=225). John S. Sundy, MD, PhD, with the Duke Clinical Research Unit, Duke University Medical Center, Durham, North Carolina, and colleagues reported their findings in an August 2011 issue of the *Journal of the American Medical Association* (JAMA). Patients in the trial have serum uric acid levels of at least 8.0 mg/dL.

These studies show that pegloticase is associated with[14*,15, 17]

- Immediate and sustained reductions in SUA levels
- Tophus resolution in six months
- Fewer flares
- Improved pain
- Improved quality of life

*Urate oxidase had rapid and significantly greater decreases in their blood uric acid levels than historical controls (median maximum level during treatment, 2.3 vs 3.9 mg/dL, P <0.001)
Case #1: Samuel

Samuel is a 77-year-old male who was diagnosed with gout at age 45. He is now having recurrent flares of gout that last three to four weeks at a time. He has large tophi on his first metatarsophalangeal (MTP) joints, over his Achilles tendons, over his patellae, and on his fingers and forearms. An attempt to surgically remove one of his tophi three years ago resulted in a severe gout flare and was complicated by infection. That tophus has subsequently recurred. Frequent gout flares and the tophi in his hands are significantly disabling. He had a severe cutaneous reaction to allopurinol in the past and refuses to take febuxostat because each time he takes it he gets a severe gout flare. His SUA is 10.4 mg/dL and his serum creatinine is 1.9 mg/dL.

Treating Samuel

Samuel would benefit from education regarding the potential for gout flares while on ULT. Considering his creatinine clearance of 31 ml/min, he should be prescribed colchicine 0.6 mg a day for two weeks before starting ULT and the colchicine should be continued after starting ULT. He should be instructed to take prednisone 20 mg at the first hint that he is developing a gout flare, because if he takes it soon enough after symptoms begin, one dose may be sufficient to
abort the attack. If the flare continues, he should take prednisone 20 mg orally twice a day until his symptoms have been completely resolved for at least a week. The choice of ULT for him is between febuxostat and pegloticase. Because of his disabling tophaceous disease, pegloticase would be the first choice since it could eliminate the visible tophi in perhaps three to six months.

Case #2: Marjory

Marjory is a 76-year-old woman who was diagnosed with gout six years ago. She has developed tophi on her fingers and toes. On two occasions the skin over the tophus on her right index finger has broken down allowing extrusion of the contents. Because of the tophi on her feet, she cannot wear shoes. She has had six gout flares in the past year. Her SUA is 8.2 mg/dL on allopurinol 300 mg a day. Her serum creatinine is 1.4 mg/dL.

Treating Marjory

The most important consideration in the management of this patient may be the potential for allopurinol dose escalation, because inadequate escalation of allopurinol is the primary cause of treatment failure for patients with gout. The limitation on allopurinol daily dosing is 800 mg. The most conservative recommended course of therapy in the primary care setting is to increase the dose of allopurinol by increments of 100 mg approximately every two weeks until the dose that lowers the serum uric acid to a level below 6.0 mg/dL has been determined. However, because this patient has disabling tophaceous disease, it would be beneficial to attain an even lower SUA level, since this is the faster pathway to tophi resolution. Thus, pegloticase should strongly be considered for this patient.

Another important consideration for this patient is the use of allopurinol in patients with renal dysfunction. Allopurinol is metabolized in the liver to oxypurinol and has a half-life of four hours. Oxypurinol also is an inhibitor of xanthine oxidase and is eliminated from the body through the kidneys. Thus, as renal function deteriorates, oxypurinol is retained in the body. Therefore, patients with lower creatinine clearance may achieve target serum uric acid levels with lower doses of allopurinol than the doses required when kidney function is normal.
Guidelines for dosing allopurinol in patients with poor kidney function have been published.[18] However, if these are adhered to, a SUA of less than 6.0 mg/dL is attained only 19% of the time.[19] It is also important to note that allopurinol has been safely escalated to reach that target in patients with kidney dysfunction.[20]

**Practice Points**
- Monitor patients closely for signs of refractory gout
- When using pegloticase
  - Rule out glucose-60-phosphate dehydrogenase (G6PD) deficiency before initiating pegloticase
  - Monitor for infusion reactions and side effects
  - Check SUA levels before each infusion—if not low (eg, less than 6.0 mg/dL), discontinue therapy
  - When using biologics, stop if little or no result after two infusions
- Do not use pegloticase in combination with a xanthine oxidase inhibitor
  - If an allergic reaction occurred, one would not know which medication caused it
  - More importantly a xanthine oxidase inhibitor may lower the UA below 6.0 mg/dL, which may encourage the use of a biologic when it is not indicated

**Summary/Conclusion**
- Use biologics to reduce SUA and resolve of tophi in patients with refractory gout
- When treating refractory gout patients with biologics, monitor closely and address adverse reactions quickly
- Provide prophylaxis against flares when starting biologics for refractory gout
References

