Latest evidence on gout management: what the clinician needs to know

Christopher M. Burns and Robert L. Wortmann

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Abstract: Until recently, the last drug approved for the treatment of gout by the United States Food and Drug Administration was allopurinol in 1966. Since 2008, two new drugs for the treatment of gout, febuxostat and pegloticase, have been approved in the US. Febuxostat has been approved in the EU and pegloticase approval is anticipated. A new single-ingredient colchicine preparation is available in the US, and the treatment recommendations for the use of colchicine in acute gout have evolved, now favoring a low-dose regimen. Several other exciting drugs are in development. Herein, we review some of basic principles in the diagnosis and staging of gout. We then examine current treatment principles, with particular attention to febuxostat and pegloticase, offering suggestions as to where they might fit into a modern therapeutic algorithm for gout treatment. We then present available data on several exciting new agents in development, including interleukin-1 inhibitors, and relate them to advances in our understanding of gout pathogenesis. We conclude with some important nonpharmacologic principles for optimal management of this ancient and eminently treatable disease. Dedicated gout research, going on quietly in the background of other breathtaking advances in rheumatology, is now paying off. This comes at a time when the number of patients affected by gout continues to rise, mainly due to an epidemic of obesity. An effort to improve lifestyle choices as a society and better management of the disease by clinicians should have a positive impact on gout incidence and outcome in our lifetimes.

Keywords: febuxostat, gout, hyperuricemia, inflammasome, interleukin-1, pegloticase, uric acid

Introduction

After an over 40-year hiatus during which no new drug had been approved, there has been a recent burst of activity in drug development for the treatment of gout [Burns and Wortmann, 2011]. In this review, we first update some basic principles in the diagnosis and staging of gout, as an understanding of the various phases of the gouty diathesis is critical for deciding whether to treat and what to use. We then review treatment, introducing the recently approved drugs febuxostat and pegloticase, suggesting where they might fit into a modern therapeutic algorithm for the treatment of gout. We then briefly discuss several exciting new agents in development for gout, including interleukin-1 (IL-1) inhibitors. Finally, we close with some important nonpharmacologic principles for optimal management of this ancient and eminently treatable disease. Therapeutic and

lifestyle choices hopefully will have a positive impact on gout incidence and outcome in our lifetimes.

Diagnosis and staging of gout

The natural history of gout progresses through asymptomatic hyperuricemia, acute gout, intercritical gout, and chronic gout. Asymptomatic hyperuricemia occurs when the serum urate is high in the absence of gout or uric acid nephrolithiasis. Most people with hyperuricemia never develop clinical gout. In those who do, asymptomatic hyperuricemia often lasts up to 20 years before the initial attack, usually occurring between the ages of 40 and 60 in men and after age 65 in women. Onset in young adulthood is often related to an inherited defect in purine metabolism or renal urate transport.

Correspondence to:
Christopher M. Burns, MD
Dartmouth Medical
School, Rheumatology,
One Medical Center Drive,
Lebanon, NH 03768, USA
Christopher.M.Burns@Hitchcock.ORG

Robert L. Wortmann, MD
Dartmouth Medical School
and Dartmouth Hitchcock
Medical Center, Lebanon,
NH, USA

Figure 1. The clinical diagnosis of gout. (A) Podagra, or acute monoarticular inflammatory arthritis of the first metatarsophalangeal (MTP) joint. Reproduced from Jelley, MJ; Wortmann, R.: Practical steps in the diagnosis and management of gout. *BioDrugs* 2000 14: 2: 99-107, with permission from Springer International Publishing AG (© 2000, all rights reserved). (B) A gout patient with numerous subcutaneous tophi on the palmar aspect of the fingers. (C) Monosodium urate crystals viewed under the polarizing microscope. (D) X-ray demonstrating typical gouty erosions at the first MTP joint, with well-demarcated erosions, away from the joint line, some with overhanging edges, and adjacent hazy tophaceous material. [Courtesy of Dr Douglas Goodwin, Dartmouth Hitchcock Medical Center, Lebanon, NH.] (E) Ultrasound images showing the double contour sign of gout in a first MTP joint [arrow] with a heterogeneous, hyperechoic tophus (beneath asterisk) within a hypoechoic effusion (dark area). (F) A cluster of tophi (arrow) in the olecranon bursa of a gout patient. (Images in E and F Courtesy of Dr John Yost, Dartmouth Hitchcock Clinic, Manchester, NH.)

The second stage of gout is heralded by the first acute attack of gouty arthritis. Most early gout attacks are monoarticular (85–90% of first attacks), often involve the lower extremities, especially the first MTP joint (known as podagra), are abrupt in onset, and are very painful (Figure 1). Podagra occurs at some point in 90% of patients. Eventually any joint may be involved. Untreated, the attacks often become polyarticular, may be associated with fever, occur more frequently and last longer, sometimes never completely resolving. In the third phase, chronic, persistent arthritis

ensues with superimposed acute attacks, tophi become visible, and progressive joint damage develops.

The differential diagnosis of acute gout is usually infectious arthritis or other crystal-induced synovitis, particularly pseudogout. The definitive diagnosis of gout is best established by aspiration of a joint or tophus and identification of needle-shaped monosodium urate crystals, preferably intracellular, with bright, negative birefringence on compensated polarized light microscopy.

Various alternatives have been proposed for a presumptive diagnosis in the absence of crystal identification [Wallace *et al.* 1967, 1977; Zhang *et al.* 2006a]. These criteria all have limitations, and crystal identification in a compatible clinical situation remains the gold standard.

The use of ultrasonography to diagnose acute and chronic gout is increasing (Figure 1). The characteristic findings are a superficial, hyperechoic, irregular band on the surface of articular cartilage, the so-called 'double contour sign' or 'urate icing', and nonhomogeneous tophaceous material surrounded by an anechoic rim. MRI and CT are even more sensitive than ultrasound at detecting gout [Thiele and Schlesinger, 2007; Wright *et al.* 2007; Dalbeth and McQueen, 2009].

Intercritical gout refers to the period between attacks during which the patient is again asymptomatic. Most patients will suffer a second attack within 2 years. The diagnosis of gout in an asymptomatic, hyperuricemic patient with a suspicious history can be difficult. Interestingly, aspirating during this phase still reveals monosodium urate crystals in 12.5–90% of joints, often associated with mild synovial fluid leukocytosis, suggesting ongoing inflammation and possible damage even during this 'quiescent' period [Pascual *et al.* 1999].

Some patients will progress to a persistent polyarticular phase of chronic gout, with no pain-free intervals, wherein the daily symptoms are difficult to distinguish from other forms of chronic arthritis, including rheumatoid arthritis and osteoarthritis. The time between initial attack and chronic gout is variable in studies of untreated patients, but the average is 11.6 years [Hensch, 1936]. If hyperuricemia persists, the total body urate load expands, and crystals deposit in cartilage, synovial membranes, tendons, soft tissues, and elsewhere. These crystal aggregates, called tophi, enlarge insidiously from microscopic in size to easily visible (Figure 1). Tophi themselves are generally painless, but they can trigger local inflammation, sometimes not readily apparent. Without treatment, joint destruction and large tophi deposition can result in grotesque deformities and progressive crippling as a result of the chronic inflammation surrounding the tophi. Skin overlying the tophus may ulcerate and extrude white, chalky or pasty material composed of urate crystals. Typical radiographic changes at this stage include

erosions of bone, sometimes difficult to distinguish from other types of erosions. A thin, overhanging, calcified or sclerotic edge is strong evidence of gout (Figure 1). As noted, ultrasonography, magnetic resonance imaging, and computed tomography can demonstrate tophi well [Thiele and Schlesinger, 2007; Wright *et al.* 2007; Dalbeth and McQueen, 2009].

Treatment of gout

The goals of treatment in gout are straightforward, but depend greatly on the stage of the gouty diathesis [Burns and Wortmann, 2012]. They are:

1. stop the acute attack as quickly as possible;
2. prevent recurrent attacks;
3. prevent or reverse complications resulting from chronic hyperuricemia and urate deposition;
4. address common comorbidities, including obesity, hypertriglyceridemia, and hypertension.

Asymptomatic hyperuricemia

Hyperuricemia *per se* is not an indication for specific urate lowering therapy (ULT), but should prompt a search for previously unsuspected medical conditions, identifiable in 70% of such patients by history and physical examination alone. Consensus on treatment of asymptomatic hyperuricemia is lacking. Hyperuricemia may be an independent risk factor for coronary artery disease. To date, there is no conclusive data that its correction reduces that risk, although evidence is mounting [Kim *et al.* 2010]. Other studies have indicated that treatment of asymptomatic hyperuricemia may prevent progression of renal insufficiency [Perez-Ruiz *et al.* 2000; Siu *et al.* 2006]. Hyperuricemia is very commonly seen in patients with metabolic syndrome, which includes obesity, hypertension, hyperlipidemia, type II diabetes, and coronary artery disease. These comorbidities should be addressed directly.

Treatment of acute gouty arthritis

Several drugs are effective for terminating the acute gouty attack. Colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids are standard approaches. Adrenocorticotrophic hormone (ACTH) is also very effective, but has become increasingly scarce or too expensive to be

a practical alternative in the US. Regardless of the particular agent chosen, the sooner these drugs are started, the more rapid the response. If a patient cannot take NSAIDs or colchicine, the choice is among oral, intra-articular or parenteral glucocorticoids. Local application of ice packs may help control pain. In some cases, analgesics, including opioids, may be added. Drugs that affect serum urate concentrations, including anti-hyperuricemic agents, should not be changed, started, or stopped during an attack, as this may worsen the inflammatory response already in progress.

Colchicine

For years, the typically recommended regimen for colchicine in acute gout was 0.5 or 0.6 mg taken hourly until joint symptoms eased; nausea, vomiting, or diarrhea developed; or the maximum 10 doses had been taken. Failure to respond spoke against the diagnosis of gout. Dosing every 2–6 hours has long been known to reduce side effects [Kim *et al.* 2003]. The prevailing recommendation, including from a European League Against Rheumatism (EULAR) panel of experts and the US Food and Drug Administration (FDA), is now for a low-dose regimen, starting with 1.2 mg, followed only by 0.6 mg in 1 hour, for a total of 1.8 mg of colchicine per day per gout attack [Zhang *et al.* 2006b]. This approach was validated in a randomized controlled trial (RCT) of 184 patients with acute gout flares of less than 12 hours duration comparing low-dose to high-dose colchicine (4.8 mg total over 6 hours) and placebo [Terkeltaub *et al.* 2010]. The low-dose approach resulted in comparable peak plasma concentrations and efficacy (50% reduction in pain within 24 hours) with a side-effect profile similar to placebo. However, over 30% of patients failed to achieve the primary endpoint in both treatment arms, and colchicine dosing for attacks of greater duration remains unclear.

In 2009, the FDA approved Colcris® (URL Pharma, Philadelphia, PA, USA) as a single-ingredient oral colchicine for gout and Familial Mediterranean Fever. The FDA has now prohibited unapproved single-ingredient colchicine preparations other than Colcris. The use of intravenous colchicine was banned by the FDA in 2008.

Colchicine peak plasma concentrations occur 2 hours after oral administration with a half-life of

4 hours, but the drug is detectable in neutrophils up to 10 days after a single dose. Colchicine has a low therapeutic index, with toxic effects occurring at approximately 3 ng/ml, the upper limit of the therapeutic range [Molad, 2002]. In most patients, side effects precede or coincide with improvement in joint symptoms. The side effect rate of 50–80% of patients using various high-dose regimens will decrease with adoption of the low-dose regimen. The drug should be stopped promptly with the onset of side effects, usually gastrointestinal, including nausea, vomiting, and diarrhea. The drug is contraindicated in patients taking clarithromycin and should be used cautiously in those with severe renal or hepatic impairment.

Colchicine inhibits acute inflammatory responses by a variety of effects, including inhibiting neutrophil adhesion, motility, and chemotaxis. It also inhibits phospholipase A₂ activation, elaboration of platelet-activating factor and leukotriene B₄, and mast cell histamine release, and downregulates tumor necrosis factor (TNF)- α receptors on macrophages and endothelial cells [Molad, 2002]. Colchicine has long been known to interfere with IL-1 β production [Di Giovine *et al.* 1987]. More recently, colchicine's inhibition of the assembly of the NLRP3 inflammasome in monocytes in response to uric acid crystals, possibly through failure to deliver the phagocytosed crystals intracellularly due to microtubule inhibition, has gained favor as a key mechanism of its action [Martinon *et al.* 2006].

NSAIDs

Once a gout attack is well underway, the preferred agent is an NSAID. In the United States indomethacin is the standard choice at an initial dose of 50–75 mg, followed by 50 mg every 6–8 hours, with a maximum dose of 200 mg in the first 24 hours. Doses as low as 25 mg four times a day can be effective. Other NSAIDs can certainly be used with the doses being the highest approved for the particular agent. Indomethacin should be continued for an additional 24 hours after attack resolution, then tapered to 50 mg every 6–8 hours for the next 2 days to prevent relapse. Nonselective NSAIDs such as indomethacin competitively inhibit the cyclooxygenase isoenzymes COX-1 and COX-2 by blocking arachidonate binding, thereby preventing conversion of arachidonic acid to prostaglandin G₂, a first step in rapid, early inflammatory responses. Most other NSAIDs

given at full dose, even COX-2 selective agents such as celecoxib, will be effective.

Corticosteroids

For acute gout limited to a single joint or bursa, local glucocorticoid injections are usually rapidly efficacious and avoid many of the toxicity of systemic agents [Kim *et al.* 2003]. In patients who are intolerant of colchicine or NSAIDs or who have contraindications, oral, intramuscular, or intravenous glucocorticoids are often dramatically effective, albeit with the usual concerns with administration of systemic corticosteroids. Higher doses, of the order of 20–60 mg of prednisone a day or the equivalent, are often necessary to reverse an acute gout attack [Clive, 2000]. Rebound attacks after withdrawal of steroids are common, so an alternate long-term strategy should be considered when initiating corticosteroids for gout.

Prophylaxis against acute attacks

Whenever possible, prophylaxis should be given to prevent the predictable attacks triggered when gout patients begin ULT, thereby avoiding the resultant incapacitation and missed work that often leads to poor compliance. Colchicine is up to 85% effective as prophylaxis against acute gout attacks in patients beginning ULT [Yu and Gutman, 1961; Paulus *et al.* 1974; Borstad *et al.* 2004]. At doses of 0.6 mg once or twice daily, colchicine is generally well tolerated. Taken chronically, the drug may produce a reversible axonal neuromyopathy and, rarely, can cause frank rhabdomyolysis. This is usually seen in patients on concomitant statins or cyclosporine [Chattopadhyay *et al.* 2001]. Patients with severe renal insufficiency should be started at 0.3 mg a day. Low-dose NSAIDs can be used for prophylaxis in colchicine-intolerant patients, e.g. 25 mg indomethacin twice a day or naproxen 250 mg/day. In patients who cannot take colchicine or NSAIDs, the clinician is sometimes forced to use the lowest effective daily dose of corticosteroids for prophylaxis.

Continue prophylaxis until the serum urate has been maintained at the target level and there have been no attacks of gout for 3–6 months. The patient should be forewarned that prophylaxis discontinuation may lead to flares. Importantly, prophylaxis may prevent the acute inflammatory response to crystals, but will not alter crystal

deposition and ongoing joint damage, so the patient may well be unaware of progressive tophi formation and destruction of cartilage and bone. Therefore, prophylaxis should only be employed with effective ULT.

Control of hyperuricemia

When to start ULT to prevent and reverse urate deposition remains debatable. The first gout attack generally occurs after many years of hyperuricemia and so some would argue that ULT should be started immediately. However, only a minority of first attack sufferers go on to develop tophi and chronic gouty arthritis, and, rarely, some patients never experience another attack, particularly those with just mild serum urate elevations. Therefore, some clinicians believe it is best to take a wait and see approach, as once started, patients tend to stay on ULT for life. Beginning ULT after a second gout attack is easier to defend and we believe that all patients who have had three gout attacks should be started on ULT. All gout patients with tophi or nephrolithiasis should receive ULT.

ULT provides an effective means of controlling hyperuricemia and modifying the long-term ramifications of the gouty diathesis. Treatment is lifelong with a dose sufficient to maintain the serum urate below 6.8 mg/dl (404 μ mol/l), preferably below 6.0 mg/dl (357 μ mol/l). Anything short of this does not reverse the process, but merely slows the rate at which crystal deposition continues. The lower the serum urate achieved, the faster tophaceous deposits will resolve [Perez-Ruiz *et al.* 2002]. Targeting a serum urate below 6.0 mg/dl is low enough to allow for normal fluctuations yet remain below the saturation level of 6.8 mg/dl, and high enough to minimize dosing and potential toxicity. That stated, an even lower target may be appropriate in patients with visible tophi.

The choices for ULT are xanthine oxidase inhibitors, uricosuric agents, or uricases. Xanthine oxidase catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid, and is inhibited by allopurinol, oxypurinol, and febuxostat. Uricosuric agents reduce serum urate by increasing the renal excretion of uric acid, and include probenecid, sulfinpyrazone, and benzbromarone. The uricases rasburicase and pegloticase enzymatically convert urate to allantoin, which is more soluble and readily excreted in

the urine. Urate-lowering drugs are not anti-inflammatory and have no role in the treatment of acute gout.

Xanthine oxidase inhibitors or uricosuric drugs are equally effective in gouty patients who excrete <800 mg of uric acid per day and have normal renal function. Both can prevent deterioration of renal function in patients with primary gout [Perez-Ruiz *et al.* 2000]. However, a xanthine oxidase inhibitor is usually the drug of choice due to fewer restrictions in use compared with uricosuric agents. The ideal candidate for a uricosuric agent is a gouty patient who is less than 60 years old, has a creatinine clearance >80 ml/min, a uric acid excretion <800 mg/24 hours on a general diet, no history of nephrolithiasis, and is not taking more than 81 mg of aspirin a day. Uricosurics should not be used in urinary uric acid overexcretors or those with a history of renal calculi of any type. Gouty patients who excrete more than 700 mg/day of uric acid have a 35% incidence of nephrolithiasis, and the risk increases with initiation of uricosurics [Yu and Gutman, 1967]. A xanthine oxidase inhibitor is preferred in patients with tophaceous gout to avoid delivery of a high urate load to the kidney. Probenecid and sulfinpyrazone are ineffective in patients with glomerular filtration rates <50 ml/min. Patients who do not achieve a serum urate concentration <6 mg/dl on uricosurics or are intolerant should move on to a xanthine oxidase inhibitor. Xanthine oxidase inhibitors and uricosuric drugs may be used in combination, but this is rarely necessary when the drugs are dosed properly.

Xanthine oxidase inhibitors

Allopurinol. Allopurinol is a substrate for xanthine oxidase, which converts it to oxypurinol, which in turn also inhibits xanthine oxidase. Allopurinol is metabolized in the liver and has a 1–3 hour half-life, while oxypurinol is excreted in the urine and has a 12–17 hour half-life. Therefore, allopurinol can be dosed once daily, with lower dosage requirements in patients with renal insufficiency, as the half-life of oxypurinol increases as the creatinine clearance decreases. The lowest dose that lowers the patient's serum urate to <6 mg/dl should be used. The usual prescribed dose is 300 mg/day, but this fails to achieve a serum urate of <6 mg/dl in 21–55% of individuals [Perez-Ruiz *et al.* 1998; Li-Yu *et al.* 2001; Becker *et al.* 2005]. Up to 800 mg/day may be required. Lower doses may be effective in patients with renal insufficiency, and

slowly increasing the dose of allopurinol to achieve a serum urate <6.0 mg/dl is not associated with an increased risk of side effects or toxicity [Dalbeth and Stamp, 2007].

The sudden lowering of serum urate after starting allopurinol or other ULT often triggers acute gout. Prophylactic colchicine or NSAID is recommended, starting 2 weeks before allopurinol whenever possible, and continuing for 3–6 months to prevent such attacks. An alternative is to start allopurinol at 50–100 mg/day and increase by similar increments weekly until the target serum urate is reached.

About 20% of patients on allopurinol report side effects and 5% discontinue, the commonest being gastrointestinal intolerance and skin rash. If the rash is mild, allopurinol can be held and the patient rechallenged after the rash has cleared. Desensitization protocols for allopurinol are effective in some patients, but cumbersome [Fam *et al.* 2001]. Other adverse reactions include fever, toxic epidermal necrolysis, alopecia, bone marrow suppression, granulomatous hepatitis, jaundice, sarcoid-like reaction, and vasculitis. Allopurinol hypersensitivity syndrome is a dreaded severe reaction that includes fever, skin rash, eosinophilia, hepatitis, progressive renal failure, and death due to multi-organ vasculitis [Hande *et al.* 1984]. Individuals with pre-existing renal insufficiency or on diuretics are at greatest risk. The risk of allopurinol hypersensitivity may correlate best with the starting dose, and that dose should be lowered based on creatinine clearance [Stamp *et al.* 2011].

There are relatively few drug–drug interactions with allopurinol, but several drugs are inactivated by xanthine oxidase, including azathioprine and 6-mercaptopurine, and their levels may become toxic in the presence of allopurinol. Allopurinol may diminish hepatic microsomal drug-metabolizing enzyme activity resulting in longer half-lives of warfarin and theophylline. Concomitant ampicillin may increase the risk of rash and cyclophosphamide the risk of bone marrow suppression with allopurinol.

Febuxostat. Febuxostat (Uloric®, Takeda Pharmaceuticals, Deerfield, IL, USA; Adenuric®, Menarini and Ipsen, EU) is a potent xanthine oxidase inhibitor that was approved in the US and Europe in 2008–9 for the treatment of gout on the basis of extensive clinical trials [Becker

Table 1. Clinically relevant data for febuxostat and pegloticase.

New drug	Febuxostat	Pegloticase
Description	Non-purine analog xanthine oxidase inhibitor	PEGylated mammalian (porcine-like) recombinant uricase
Phase III trials (total n)	3 trials ($n = 4103$ patients)	2 replicate trials ($n = 212$)
Approved	EMA: 5/2008 FDA: 2/2009	FDA: 9/2010 EMA: Not approved
Dosing	EMA: 80 or 120 mg po qd FDA: 40 or 80 mg po qd	8 mg IV every 2 weeks
Common adverse events	Gout flares, liver function test abnormalities, diarrhea, headache, dizziness, musculoskeletal symptoms, abnormal thyroid tests, possible increased cardiovascular risk	Gout flares (80%), infusion reactions (25%), anaphylaxis (5%); musculoskeletal symptoms, ecchymosis, nausea, vomiting, headache, nasopharyngitis, constipation, nephrolithiasis, infection, chest pain, exacerbation of congestive heart failure
Potential advantages	Less dose adjustment to achieve target serum urate, no adjustment for creatinine clearance over 30 ml/min, appears to be safe for those with allopurinol hypersensitivity	Only for those who have failed or cannot take all other urate-lowering therapy
Ideal candidates	Patients who are intolerant of allopurinol including those with hypersensitivity, have failed other urate-lowering therapy, have renal insufficiency with creatinine clearance over 30 ml/min.	Patients with advanced, chronic, tophaceous gout who have failed or are intolerant of all other urate-lowering therapy; best used as debulking agent followed by conventional therapy if possible.

et al. 2005, 2009, 2010; Schumacher *et al.* 2008, 2009]. It is of a different chemical class than allopurinol and a more selective inhibitor of enzyme activity. It appears to be an excellent alternative for allopurinol-intolerant patients. Febuxostat was more effective than allopurinol in lowering serum urate levels in trials, but importantly, allopurinol doses used were fixed and too low. The true comparative efficacy of these agents remains unknown. Gout flares were more frequent with febuxostat, and patients should be prophylaxed for up to 6 months after initiation. Dosing in the US is 40 or 80 mg daily, and in Europe 80 and 120 mg daily. Mild to moderate renal insufficiency (creatinine clearance >30 ml/min) does not require dose adjustment. As with allopurinol, febuxostat should not be used with drugs metabolized by xanthine oxidase, including azathioprine and 6-mercaptopurine.

Febuxostat and allopurinol have similar safety profiles. Common febuxostat side effects in the

clinical trials included diarrhea, dizziness, headache, liver function test abnormalities, and altered thyroid function tests. Cardiovascular events were more frequent with febuxostat, but accounting for total drug exposure, the incidence was the same as in comparator arms. The European Medicines Agency (EMA) recommendation is not to use febuxostat in patients with ischemic heart disease or congestive heart failure. Although a final phase III trial did not detect increased cardiovascular risk [Becker *et al.* 2010], the FDA has required cardiovascular postmarketing surveillance by the manufacturer.

The ideal candidate for febuxostat is a gouty patient with intolerance of allopurinol, hyperuricemia not controlled with other urate-lowering therapy, or mild renal insufficiency (Table 1). Febuxostat should be tried before allopurinol desensitization. One study has shown that patients with previous allopurinol hypersensitivity were able to tolerate febuxostat [Becker *et al.* 2006].

Febuxostat is preferred over uricosuric agents in patients with nephrolithiasis.

Uricosuric agents

Uricosuric agents increase the renal excretion of uric acid. Separate transport systems for the secretion and reabsorption of organic ions, including uric acid, exist in the kidney. Reabsorption of urate by renal tubular brush border anion transporters can be inhibited by uricosuric agents which compete with urate for those transporters in the tubule lumen. This inhibition requires high doses of uricosuric agents.

Probenecid is now the only uricosuric agent available in the US. Benzbromarone is used in some other countries. Many other medications also reduce serum urate levels by enhancing the renal excretion of uric acid. Probenecid is well-absorbed orally with a dose-dependent half-life in plasma of 6–12 hours, which is prolonged by concomitant use of allopurinol. Probenecid is metabolized in the liver with <5% of the administered dose recovered in urine. A total daily dose of 500–3000 mg is administered in two or three divided doses. Initiation may precipitate gout flares, and, as with all uricosuric agents, probenecid increases the risk of renal calculi. Up to 18% of patients develop gastrointestinal side effects, and 5% develop hypersensitivity and rash. Serious toxicity is rare, yet still about one third of patients will eventually become intolerant and discontinue probenecid. Probenecid alters the metabolism and increases the potency of many drugs, such as penicillin, methotrexate, and NSAIDs, by decreasing their renal excretion, metabolism, or hepatic uptake. Potential drug interactions should always be considered when starting a patient on probenecid.

Benzbromarone is more potent than probenecid and sulfinpyrazone [Perez-Ruiz *et al.* 1998, 2000]. It is well-tolerated and effective in cyclosporine-treated renal transplant patients. It can be used in patients with a creatinine clearance as low as 25 ml/min. Hepatotoxicity has led to its removal from some markets worldwide, but the true risk remains controversial [Perez-Ruiz *et al.* 1998; Lee *et al.* 2008].

Uricases

Humans lost uricase during evolution due to a missense mutation in the gene encoding the enzyme [Wu *et al.* 1989]. In many other species,

uricase converts urate to allantoin, which is readily excreted in the urine. Rasburicase is a recombinant uricase cloned from *Aspergillus flavus* approved for use in tumor lysis syndrome. Despite reports of its efficacy [Richette *et al.* 2007], approval for use in gout has not been pursued due to its short half-life and immunogenicity.

Pegloticase. Pegloticase (KRYSTEXXA[®], Savient Pharmaceuticals, East Brunswick, NJ, USA) is a pegylated mammalian (porcine-like) recombinant uricase. Recently approved in the US for the treatment of severe tophaceous gout. It is given at a dose of 8 mg every 2 weeks by IV infusion [Sherman *et al.* 2008; Burns and Wortmann, 2011]. The enzyme activity half-life is 6.4–13.8 days. Serum urate falls dramatically in 24–72 h, often to 1.0 mg/dl, and stays low for 21 days [Sundy *et al.* 2007]. Pegloticase was studied in just over 250 patients in phase II and III trials prior to its approval in the US in late 2010 [Sundy *et al.* 2008, 2011; Baraf *et al.* 2008a]. In phase III trials of 212 subjects with treatment failure gout, pegloticase at 8 mg every 2 or 4 weeks was significantly more effective than placebo at achieving the primary endpoint of a plasma urate concentration < 6 mg/dl (357 μ mol/l) [Sundy *et al.* 2011]. Pegloticase was also capable of reducing tophi rapidly [Baraf *et al.* 2008a, 2008b]. However, despite specific prophylaxis, gout flares, infusion reactions, and serious adverse events were significantly more frequent in patients receiving pegloticase. The most common reason for withdrawal was infusion reaction.

The development of high-titer antibodies to pegloticase in treated patients is associated with loss of response and infusion reactions [Becker *et al.* 2008]. In fact, 96% of patients with antibodies to the poly(ethylene glycol) portion of the drug became nonresponders, and 50–76% had infusion reactions. These antibodies do not inhibit uricase activity *in vitro*. Development of these antibodies heralded a rise in serum urate levels and stopping pegloticase when serum urate levels rose above 6 mg/dl would have avoided 91% of infusion reactions [Wright *et al.* 2009]. Accordingly, the FDA recommends clinicians stop pegloticase if the serum urate rises above 6.0 mg/dl during ongoing treatment. In open-label extension trials, gout attacks continued to decline, most patients maintained target serum urates, and more patients had tophus resolution [Sundy *et al.* 2009]. Unfortunately, infusion reactions continue to occur, often resulting in discontinuation.

Pegloticase is appropriate for patients with tophaceous gout with persistent gout attacks or damaging arthropathy who have failed or are intolerant of conventional therapy (Table 1). Presumably, many such patients will now be eligible for and respond to febuxostat, but others will not and may receive pegloticase. A good way to conceptualize pegloticase is as a urate debulking agent, emphasizing it as adjunctive therapy that should be followed by other ULT whenever possible. Pegloticase could conceivably be used to reduce tophi more quickly than conventional treatment when that is felt to be necessary. Continuous use will be restricted by its immunogenicity. Over 25% of patients develop antibodies, infusion reactions, restricted efficacy, and/or drug withdrawal. There is a 5% anaphylaxis rate. Gout flares are almost certain, can be severe, and occur despite prophylaxis. Concomitant infusions of corticosteroids are required to ameliorate infusion reactions with pegloticase and may further restrict its use. Finally, pegloticase cannot be given to patients with glucose-6-phosphate-dehydrogenase deficiency as it may induce hemolysis. As for a potential cardiovascular signal in the clinical trials, the FDA's own independent analysis could not verify an increased risk.

Despite these downsides, the target patient for this drug is often miserably symptomatic and often has no other options. Monitoring for a rising serum urate level as a sign of antibody development and impending infusion reaction will allow for safer administration [Wright *et al.* 2009]. A recent report described a group of patients who were safely maintained on pegloticase alone for a median follow up of 2.5 years [Hamburger *et al.* 2010]. The frequency of infusion reactions was low in this group, even in subjects with up to 6-month breaks between infusions. Nevertheless, this drug has significant potential toxicity and should only be administered at experienced infusion centers capable of dealing with serious reactions, including anaphylaxis.

Drugs in development

IL-1 Inhibitors

Elegant studies in the mouse demonstrated 25 years ago that IL-1 is an important mediator of the early inflammatory response to monosodium urate crystals *in vivo* [Di Giovine *et al.* 1987; Malawista *et al.* 2011]. More recently, IL-1 receptor (IL-1R)-deficient mice and mice

treated with an IL-1 inhibitor (Rilonacept) had significantly reduced inflammation in response to intra-articular injection of urate crystals [Martin *et al.* 2009; Torres *et al.* 2009]. We now know that the innate immune system responds to a variety of pathogens and endogenous molecules, the latter including urate crystals, through recognition of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). Recognition of these patterns occurs through germline-encoded, or innate, pattern recognition receptors (PRRs). NLPR3, one of several intracellular macromolecular platforms termed inflammasomes, is activated through this pathway and plays a key role in the IL-1 response in gout [Martinon *et al.* 2006].

The current paradigm (Figure 2) suggests that monosodium urate crystals bind innate immune system receptors, including Toll-like receptors (TLRs) 2 and 4, on the cell surface of monocytes, leading to enhanced transcription of pro-IL-1 β and phagocytosis of the crystals [Chen *et al.* 2006; Scott *et al.* 2006]. The phagocytosed crystals then stimulate the assembly of the NLPR3 inflammasome by an as yet undefined pathway, and thus subsequent activation of caspase-1 [Martinon *et al.* 2006; Kingsbury *et al.* 2011]. Activated caspase-1 then cleaves pro-IL-1 β to active IL-1 β . Secreted IL-1 β then binds to IL-1R on local endothelial cells and macrophages, signaling them to produce further pro-inflammatory cytokines and chemokines, including TNF- α , IL-6, and neutrophil chemoattractants [Liu-Bryan *et al.* 2005; Di Giovine *et al.* 2006; Chen *et al.* 2006]. These amplify the response, attracting other inflammatory cells, including neutrophils, into the area.

Proof of concept has been established in clinical trials of several IL-1 inhibitors, both for treatment and prophylaxis of gout flares. These agents include anakinra, an IL-1R antagonist, rilonacept, an IL-1 decoy receptor, or Trap, and canakinumab, an anti-IL-1 β monoclonal antibody. Note that anakinra and rilonacept inhibit both IL-1 α and IL-1 β function. In the earliest published study, anakinra, FDA-approved for the treatment of rheumatoid arthritis (Kineret[®], Amgen, Thousand Oaks, CA, USA; Swedish Orphan Biovitrum, Stockholm, Sweden), was very effective at 100 mg subcutaneously daily for 3 days in 9 of 10 patients with acute gout at day 3 [So *et al.* 2007].

Figure 2. Initiation of the inflammatory response to monosodium urate crystals (MSU) by the innate immune system. MSU are recognized as danger-associated molecular patterns (DAMPs) by innate immune receptors, including Toll-like receptors (TLRs), on monocytes. A dual signaling process begins. One pathway, involving the adapter protein used by TLRs, MyD88 [myeloid differentiation primary response gene 88], leads to translocation of activated NFκ-β (nuclear factor κ-β) to the nucleus where it activates transcription of pro-IL-1β. Simultaneously, phagocytosis of MSU and processing by the phagosome and lysosome results in assembly and activation of the NLRP3 inflammasome in a cathepsin-B and K⁺ flux dependent fashion. As a result, pro-caspase-1 is cleaved to active caspase-1, which in turn cleaves the nascent pro-IL-1β to its active form, which is secreted into the cellular milieu. [IL-18 is released in a similar fashion.] Binding of IL-1β to its receptors on local macrophages and synoviocytes activates a signaling pathway that includes MyD88 and IRAK-4 (ILR1-receptor associated kinase), resulting in NFκ-β activation and translocation to the nucleus. There, NFκ-β mediates transcription of multiple inflammatory cytokines and chemokines, thus greatly amplifying the original danger signal. Other cells are recruited to the area, including neutrophils, and a full blown attack of gout ensues. ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase recruitment domain.

Rilonacept. Rilonacept (Araclyst[®], Regeneron Pharmaceuticals, Tarrytown, NY, USA) was approved by the FDA in 2008 for children with the autoinflammatory cryopyrin-associated periodic syndromes (CAPSs). In a pilot 14-week, nonrandomized study, 10 patients with treatment failure chronic gout received rilonacept 320 mg subcutaneously, followed by 160 mg subcutaneously per week for 5 weeks [Terkeltaub *et al.* 2009]. Median pain scores decreased significantly after 2 weeks, and that effect was maintained at 8 weeks. Five of the 10 patients had more than 75% improvement. In a phase II RCT,

hyperuricemic patients with at least two gout attacks per year were started on allopurinol. For flare prophylaxis, patients were randomly assigned to either rilonacept 160 mg subcutaneously per week or placebo [Schumacher *et al.* 2012]. During the 16-week trial, 39/42 patients receiving placebo had flares *versus* 9/41 patients receiving rilonacept ($p = 0.0036$). Adverse events were similar and not serious in both groups. A RCT of the safety and efficacy of rilonacept for acute gout flare compared with indomethacin and both rilonacept and indomethacin has been completed, but the results have not yet been

reported. Other studies are active (see <http://clinicaltrials.gov/ct2/results?term=rilonacept>).

Canakinumab. Canakinumab (Ilaris®, Novartis Pharma AG, Basel, Switzerland) is a fully human monoclonal anti-IL-1 β antibody with a 28-day half-life that was approved by the FDA and EMEA in 2009 for CAPS. In an 8-week, multicenter RCT, 147 patients with acute gout, refractory or with contraindications to NSAIDs and colchicine, received one subcutaneous injection of canakinumab at various doses, while 57 similar patients received a single intramuscular injection of 40 mg triamcinolone acetonide (TCA) [So *et al.* 2010; Schlesinger *et al.* 2011a]. The canakinumab 150 mg dose was significantly more effective than TCA at reducing pain and did so more rapidly. In the canakinumab group, only 3.7% of patients experienced another flare over the trial period, whereas 45.4% of patients given TCA had another flare ($p = 0.006$). A recently published study examined canakinumab as flare prophylaxis in 437 patients starting allopurinol [Schlesinger *et al.* 2011b]. The 16-week RCT randomized patients to single doses of canakinumab ranging from 25 to 300 mg, or 4 weekly shots (50 mg, 50 mg, 25mg, 25 mg), or colchicine at 0.5 mg a day. At doses over 50 mg, the mean number of flares per patient and the risk of experiencing at least one flare were both significantly reduced (~60–70%) in the canakinumab *versus* the colchicine group. Presented with these and other as yet unpublished data (see <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM259596.pdf>), a FDA advisory board recommended against the proposed approval of canakinumab for acute gout in patients who cannot tolerate NSAIDs or colchicine. The board cited too many safety concerns, including infection, cardiovascular and renal risk, and inadequate pharmacokinetic data in older patients. Several trials are planned or underway for canakinumab in gout (see <http://clinicaltrials.gov/ct2/results?term=canakinumab>).

Despite this setback, it seems probable that canakinumab or another IL-1 inhibitor will ultimately be approved for the treatment of acute gout and/or prophylaxis for gout flares in those starting ULT. There is a definite need in this area as there are many gout patients who have failed or cannot take colchicine or NSAIDs, and whose only option remains corticosteroids, a problematic approach.

Better uricosurics

Most patients with gout have inefficient renal excretion of uric acid as the mechanism of hyperuricemia [Wyngaarden and Kelley, 1976; Simkin, 2003]. The readily available uricosuric, probenecid, and the variably available sulfinpyrazone and benzbromarone, are now known to inhibit uric acid reabsorption by URAT1, the major transporter of uric acid from the renal proximal tubule [Enomoto *et al.* 2002; Endou and Anzai, 2008]. However, they also inhibit transporters on the basolateral aspect of the renal epithelial cell, including OAT4 and GLUT9, affecting reabsorption into the circulation [Burns and Wortmann, 2011]. A newly developed uricosuric now in clinical trials, lesinurad (RDEA594; Ardea Biosciences, San Diego, CA, USA), has specificity for URAT1, and does not significantly affect other transporter [Anzai *et al.* 2008; Dalbeth and Merriman, 2009]. The chief advantage of this is a lack of the drug interactions seen with other uricosurics. In addition to being developed as a standalone uricosuric, the investigators are emphasizing the use of diuretics such as lesinurad in combination with a xanthine oxidase inhibitor to more effectively lower serum urate in gout, an approach previously reported to be effective [Perez-Ruiz *et al.* 2002; Goldfarb and Smythe, 2007]. Several lesinurad combination clinical trials are underway (see <http://clinicaltrials.gov/ct2/results?term=RDEA594>).

Recently presented data on Ardea's related compound, RDEA3170, demonstrated this newer agent's high potency due to direct binding and functional inhibition of URAT1. All known URAT1 inhibitors probably bind in the same general area within the molecule, but each inhibitor binds a specific, yet overlapping set of residues, and this accounts for major differences in inhibition of URAT1, at least *in vitro*. For example, RDEA3170 is equipotent to benzbromarone, but 200 times more potent than sulfinpyrazone and 500 times more potent than probenecid in *in vitro* assays [Tan *et al.* 2011]. RDEA3170 has not been used in any clinical trials yet, but the fine tuning of the specificity and potency of URAT-1 inhibition at a molecular level now seems within reach. These potent uricosurics would be contraindicated in patients with urate nephrolithiasis, and if they deliver the dramatic drops in serum urate promised, alone or in combination, prophylaxis for the inevitable gout flares will be essential.

Along similar lines, arhalofenate is a novel oral agent in development as an insulin-sensitizer for

type II diabetes. Serendipitously, *in vitro* studies found arhalofenate to be a uricosuric that inhibits URAT-1. In analysis of two of their phase II diabetes trials in which serum urate levels were obtained, in patients with a baseline serum urate ≥ 6.0 mg/dl (mean 6.8–7.1 mg/dl), arhalofenate at doses of 200 mg ($n = 29$), 400 mg ($n = 37$), and 600 mg ($n = 35$) resulted in 48%, 78%, and 83% of patients achieving a serum urate target of < 6.0 mg/dl versus 25% in the placebo group ($n = 61$) [Gopal *et al.* 2011]. The drug was well tolerated and no cases of nephrolithiasis were reported. Arhalofenate may prove to be a dual-purpose drug with benefit for patients with the common comorbidities of gout and type 2 diabetes.

Novel targets

Other attractive targets for drug development in acute gout include any step along the early IL-1 β pathway. Two small molecule drugs that inhibit the active site of caspase-1, VMX-740 (pralnacasan) and VMX-765, were studied some time ago in several inflammatory conditions. Pralnacasan had unacceptable toxicity, and results of a phase II trial of VMX-740 in plaque psoriasis, completed in 2005, were never published [Cornelis *et al.* 2007; Mitroulis *et al.* 2010]. Interleukin-1 receptor-associated kinase 4 (IRAK-4) is a signaling molecule located downstream of the IL-1R. Recently presented data on a highly specific IRAK-4 small molecule kinase inhibitor demonstrated its ability to block human IL-1 responses *in vitro* and was effective in a gout-like murine peritonitis model [Bree *et al.* 2011]. The promise of a small molecule, presumably a less expensive and more convenient approach to inhibition of IL-1B pathway, would be an attractive alternative to biologics. An even more novel approach could evolve from recent evidence that activated CD4+ T cells expressing CD40 ligand (CD154) regulate the inflammasome [Guard *et al.* 2009]. *In vitro*, a CD40 ligand construct, the adiponectin fusion protein (ADIPOQ-CD40L), engages CD40 on activated macrophages and shuts off the NLRP3 inflammasome and caspase-1. This may be a mechanism by which the adaptive immune system dampens the intense innate inflammatory response to urate crystals and other ‘danger’ signals.

Compliance with treatment

Except in situations such as chronic renal failure or organ transplantation where consultation with

a rheumatologist is recommended, the available treatment for gout is so straightforward that management should be effective and outcomes excellent. Unfortunately, even in typical patients accurately diagnosed, good outcomes may be elusive. Improper prescribing or poor compliance is the usual cause of urate-lowering therapy failure. Compliance is often a problem when treating chronic asymptomatic conditions. Associated alcoholism may contribute. Perhaps more importantly, patients may have to initially take up to three different medications on different schedules for gout, and that’s confusing. Presumably, patients who understood why they were taking medications would likely be more compliant. The senior author has developed an analogy that helps some patients with compliance [Wortmann, 1998]. Whatever the technique, establishing an alliance with the patient to achieve compliance is critical. The perfect choices of therapeutics without compliance still results in treatment failure.

Other factors

Factors independent of medication and compliance may determine whether recurrent attacks, chronic gouty arthritis, nephrolithiasis, or nephropathy develops. Nowadays, strict dietary purine restriction is rarely recommended, as it lowers mean serum urate levels by only about 1 mg/dl. In fact, weight loss in an obese individual will have a greater urate lowering effect than a purine-free diet [Dessein *et al.* 2000]. The ingestion of products containing fructose sweeteners, such as soft drinks, promotes hyperuricemia [Rho *et al.* 2011]. A diet with moderately decreased calories and carbohydrates, and increased protein, dairy products, and unsaturated fats can be beneficial for the patient with gout [Dessein *et al.* 2000; Choi, 2010]. Consumption of alcoholic beverages or rich foods can trigger gout attacks in some patients, and the individual patient should avoid indiscretions known to precipitate attacks. Diet is more important in the management of other medical problems coexistent with gout, including obesity and hyperlipidemia, the latter affecting 75% of gout patients [Choi, 2010].

Alcohol consumption is an important factor in gout. Acute excesses may exacerbate hyperuricemia by causing hyperlactacidemia. Chronic alcohol ingestion can stimulate increased purine production. The more one drinks, the higher the risk [Choi *et al.* 2004]. Beer contains a large purine load and regular ingestion may contribute

to hyperuricemia and gout. Drinking beer is more likely to lead to the development of gout than drinking liquor, whereas moderate wine consumption does not increase risk [Choi *et al.* 2004]. Finally, compliance with medication is worse among patients who consume alcohol.

About one third of gouty subjects have hypertension, and that condition should be treated aggressively. Many hypertensive gouty patients require a thiazide diuretic, which will raise serum urate levels, requiring adjustment of concomitant urate-lowering therapy. Losartan is an alternate antihypertensive medication and fenofibrate is a lipid-lowering agent that have mild uricosuric activity, and may be useful adjuncts in this population [Wurzner *et al.* 2001; Yamamoto *et al.* 2001].

Future directions

Gout is an ancient malady whose incidence continues to rise despite being one of the best understood diseases in all of medicine in terms of pathogenesis and treatment [Roddy *et al.* 2007]. An epidemic of obesity and the metabolic syndrome has, in part, driven this increase. Our understanding of the biochemistry of hyperuricemia and the immunology of acute gout has increased greatly over the last few years. Febuxostat and pegloticase are now available and other new therapeutics are in the pipeline. Years of dedicated gout research are now paying off. An effort to improve lifestyle choices as a society and better management of the disease by clinicians should have a positive impact on gout incidence and outcome in our lifetimes.

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