The Year in Gout
2010-2011

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Abstract
Over the past decade, the pace of investigation in the field of gout has accelerated tremendously. New advances have led to deeper insight into the processes of inflammation and innate immunity, and new treatments are now available, or likely to become available in the near future. Some of the more interesting new findings in the field of gout are presented in the context of gout biology and treatment overall. Gout epidemiology, current understanding of renal urate handling, recent investigations into the mechanism of inflammation in acute gout, dietary factors in gout development, the potential role of hyperuricemia in cardiovascular and renal disease, and treatments that are either newly available or in development are discussed.

Over the past decade, the pace of gout research and discovery has quickened dramatically. New insights into gout biology and new approaches to gout treatment have led to a resurgence of interest among clinicians and scientists alike. Indeed, the pace of gout advances is such that it is now appropriate to examine gout progress on an annual basis, rather than as a matter of change over decades. In that spirit, we review some of the important advances made in gout over the past 12 to 18 months, presenting the new findings in the context of older knowledge, both long-established and more recently generated.

Disease Presence and Burden
Multiple studies over the past several decades indicate that the incidence and prevalence of gout have been increasing, more than doubling in the US between the 1960s and 1990s. Causes for this increase are not fully established but likely include the current epidemic of obesity, increasing consumption of fructose and beer, increased prevalence of renal insufficiency, and the general aging of the population.

Recent work suggests that gout prevalence may continue to rise. Using data from the National Health and Nutrition Survey (NHANES) (conducted by the Center for Disease Control approximately every decade, most recently in 2008),
Zhu and colleagues compared gout prevalence between NHANES III (1988-1994) and NHANES 2007-2008. Overall, gout prevalence rose from 2.7% to 3.9% in this period, making gout far and away the most common inflammatory arthritis. Increases in gout prevalence during this time were even greater for males (from 3.8% to 5.9%) and the elderly. Indeed, for individuals over the age of 80, NHANES data suggest that the prevalence of gout may now be as high as 12.6%. Increasing frequencies of obesity and hypertension may account for these trends.

The high prevalence of gout comes with costs, both in terms of human suffering and financial expense. In a recent economic analysis using insurance databases, Wu and colleagues demonstrated that the cost of medical care is as high as $25,000 annually for individuals with the most severe gout (six or more acute attacks per year), in part due to comorbidities. For individuals with less severe but still active gout (three to five attacks annually), the cost to the healthcare system was approximately $18,000 per year. For individuals without gout, health care costs were less than $5,000 per year.

Biology and Pathophysiology: Hyperuricemia

Intensive efforts over the past 5 to 10 years have begun to unravel the complex nature of renal uric acid handling. Current evidence suggests that nearly all renal urate management after filtration, including both resorption and secretion, occurs in the proximal tubule (Fig. 1).

Studies have documented the presence of multiple organic anion transporters (OATs) that resorb urate, both on the luminal and the basolateral side of the renal epithelial cells. Of these, the most important appears to be URAT1, a luminal-surface protein. Individuals with congenital URAT1 deficiencies demonstrate hypouricemia, hyperuricosuria, and in some cases exercise-induced renal failure. URAT1 blockade is now appreciated to be the mechanism of several currently-prescribed uricosuric agents, including probenecid. On the basolateral side, the transporter Glut9a also appears to play an important role in urate re-absorption. Interestingly, Glut9a and its analog Glut9b are also distributed extra-renally; whether their presence in other tissue implies a role for urate in these sites remains to be determined.

Transporters that secrete urate, moving it from the interstitium into the urinary space, participate directly in urate excretion. These include ABCG2, MRP4, NPT1, and NPT4 on the luminal side of tubular epithelial cells, and OAT1 and OAT3 on the basolateral surface. Of these, ABCG2 may be of particular importance, since hereditary deficiencies of this protein may account for as much as 10% of primary urate underexcretion, at least among Caucasian populations.

The importance of these various renal tubular transporters in setting serum urate levels has been underscored by several genome-wide association studies, designed to identify single nucleotide polymorphisms (SNPs) associated with serum urate abnormalities. One such recent study by Yang and colleagues identified SNPs associated with urate levels in greater than 28,283 patients in the Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) repository, and validated the resultant findings in the more than 22,054 patients in the Women’s Genome Health Study. Yang’s study identified eight SNPs that achieved genome-wide significance with regard to serum uric acid level, and most of these SNPs were closely associated with genes for proteins known to serve as renal urate transporters. Indeed, SNPs associated with genes for urate reuptake transporters tended to aggregate with low urate levels, whereas SNPs associated with genes for urate secretion transporters tended to aggregate with higher serum urate levels.

Biology and Pathophysiology: Inflammation

One of the most important advances in the understanding of gout over the past 10 years has been the observation by
Martinon and colleagues that monosodium urate crystals can activate the inflammasome,\textsuperscript{16} a multimolecular complex that converts pro-IL-1β and pro-IL-18 into their active forms.\textsuperscript{17}

These observations have placed IL-1, in particular, at the center of the gouty inflammatory response. How MSU crystals activate the inflammasome remains uncertain, with various studies suggesting that the process is receptor-dependent (especially toll-like receptors)\textsuperscript{18,19} or independent. Some evidence suggests that MSU crystals may act via direct interaction with plasma or vesicular membranes\textsuperscript{20,21} or through their ability to stimulate superoxide anion generation. Another possibility is that low intracellular potassium levels may lead to inflammasome triggering,\textsuperscript{22} but the steps leading to potassium depletions have been unclear. Recently, Schorn and colleagues have proposed a mechanism; they suggested that after phagocytic uptake of MSU crystals, endosomes fuse with acidic lysosomes. Exposure to an acidic environment causes a massive release of sodium from the MSU crystals. This leads to increased intracellular osmolarity and drives passive free water influx. As a result, potassium concentrations fall, triggering inflammasome activation.\textsuperscript{23}

A relatively underexplored question in gout is the mechanism of MSU crystal precipitation. Although the saturation point of urate is 6.8 mg/dL, urate is actually relatively resistant to precipitation, and many patients with serum urate levels significantly greater than 6.8 mg/dL may go for extended periods without experiencing a gouty attack. Indeed, in vitro, it may take weeks for a supersaturated solution of MSU to yield crystals. With this in mind, and with an awareness that an older literature demonstrated that MSU crystals in vitro are frequently antibody-coated,\textsuperscript{24,25} Kanevets and colleagues tested the hypothesis that MSU crystallization may be hastened by an immune response. They first confirmed that supersaturated MSU solutions crystallized only slowly. They then injected MSU crystals into mice and found that these mice (but not control mice) consistently generated a novel set of antibodies that could bind to MSU crystals in vitro. Finally, they demonstrated that these MSU-binding antibodies, when added to supersaturated MSU solutions, hastened crystal formation. When infused into B-cell deficient mice, these antibodies could markedly enhance inflammation in response to MSU crystal injection.\textsuperscript{26} Taken together, these data raise the possibility that once gout is established in a patient, an immune response to MSU crystals may serve to facilitate MSU precipitation and further, or worsen, the gouty condition.

**Diet, Hyperuricemia, and Gout**

Significant attention has been focused, of late, on the role of diet in the development of hyperuricemia. Well-established risk factors, such as purine intake and ethanol consumption, have been confirmed, and other studies suggest that fructose intake may be an important contributor to hyperuricemia.\textsuperscript{27}

However, some dietary components may actually be beneficial for lowering serum urate and reducing the risk of gouty attacks. One such component appears to be low-fat dairy products, such as yogurt and skim milk. Indeed, both epidemiologic and physiologic studies suggest a beneficial role for dairy in lowering serum urate.\textsuperscript{28,30} The most recent of these studies is a physiologic trial performed by Dalbeth and colleagues in which they administered either milk, a milk extract, or a soy control to healthy male volunteers then followed serum urate levels.\textsuperscript{31} Within 3 hours of receiving any of the dairy samples, but not the soy extract, subjects experienced a significant decline (between 10% and 15%) in serum urate levels.

The mechanism of this serum urate reduction appears to depend at least in part upon a uricosuric effect.\textsuperscript{32} Dalbeth and colleagues have recently considered the possibility that a reduction in gout attacks among dairy users might also depend on an anti-inflammatory effect of dairy. To assess this, they injected mice with MSU crystals in the presence or absence of treatment with dairy extracts. Mice who received several of the dairy extracts, including both lipid and protein fractions, experienced reduced inflammation. Thus, some elements of dairy may convey anti-inflammatory effects.\textsuperscript{33} These data suggest that patients with gout (at least those with adequate renal function) may want to consider increasing their intake of low fat dairy products.

Like milk, coffee is a beverage that may have urate lowering properties. In several studies, daily consumption of 4 or more cups of coffee daily has been associated with lower serum urate levels and a reduced risk of gout.\textsuperscript{34,35} This effect was independent of caffeine ingestion, since consumption of decaffeinated coffee conveyed the same benefit, whereas consumption of caffeinated tea did not. Indeed, in a recent study, Neogi and colleagues demonstrated that binge consumption of caffeinated coffee (or otherwise) but not non-caffeinated beverages raised, rather than lowered, serum urate and risk of gout.\textsuperscript{36} Individuals wishing to modulate their diets to lower their serum urate may, therefore, need to balance the benefits of coffee with the drawbacks of caffeine.

**Comorbidities of Gout and Hyperuricemia**

It has long been appreciated that patients with gout commonly suffer comorbidities, but the extent of these comorbidities has recently become clearer. In a database study of more than 500 gout patients, Keenan and colleagues observed that the modal number of comorbidities was 4, with some patients having as many as 7. The most common comorbidities were those associated with metabolic syndrome, including hypertension (greater than 90%), hyperlipidemia (greater than 60%), chronic kidney disease, diabetes, and coronary artery disease (the latter three all greater than 50%).\textsuperscript{37}

It has been difficult to assess whether gout and hyperuricemia either contribute to or result from these other conditions. Large epidemiologic studies and subsequent meta-analyses have indicated that hyperuricemia may convey an independent, albeit modest risk for cardiovascular (CV) disease. However, these studies may potentially understate hyperuricemia risk, since they typically correct for
other risk factors (such as hypertension) to which hyperuricemia may contribute. One way to approach this difficulty would be to lower serum urate in patients with high CV risk and follow them for events. Such an approach was taken, in retrospect, in a cohort study by Wei and colleagues. These investigators examined the rate of cardiovascular events in 7,135 patients, including 1,035 allopurinol users. They observed that allopurinol users had a significant decrease in CV events as the doses rose from 100 to 300 mg and as their urate levels fell.

In a study based on a similar principal and presented at the 2010 ACR meeting, Chen and Pan cross-referenced clinical, drug, and mortality databases to follow the CV outcomes of urate lowering among 45,215 patients in Taiwan, with a mean follow-up of 11.3 years. They observed that patients who received urate-lowering therapy experienced approximately half the cardiovascular and stroke mortality as those who did not receive urate lowering. Additionally, patients with renal failure experienced impaired risk reduction when treated with benzbromarone rather than allopurinol. Since uricosuric agents such as benzbromarone are relatively ineffective in patients with renal insufficiency, this observation suggests that urate lowering agents are only likely to prove beneficial when they actually lower urate. These data hint at a role for urate lowering in reducing cardiovascular risk, but further study is needed.

Another area of historic contention is the role of uric acid in perpetuating renal disease. While a role for renal insufficiency in hyperuricemia and gout is almost universally accepted, a role for hyperuricemia and gout in perpetuating renal insufficiency is much less well established. Recently, at least three studies have approached this question by asking what, if any, is the effect of urate lowering on renal function. In one study, Whelton and colleagues took advantage of the FOCUS, a 5-year open label trial of febuxostat at various doses for urate lowering and gout attack reduction. They re-stratified the study subjects not according to dose, but rather by the degree of urate lowering achieved, and showed that those individuals who had the greatest degree of urate lowering had a reduced progression of renal deterioration. In a similar investigation presented in abstract form, Krishnamurthy and colleagues showed that allopurinol use was associated with preserved renal function, relative to no allopurinol use. These data suggest that urate lowering may preserve renal function and imply a role for urate in promoting renal insufficiency. This interpretation would appear to be supported by a prospective trial by Goicoechea and colleagues, who enrolled 113 patients with renal disease (but no gout) and treated them with either allopurinol or placebo. Subjects who received allopurinol had a reduced rate of renal deterioration relative to the controls.

**Treatment**

In the setting of the large numbers of co-morbidities that gout patients experience, older therapies for gout may not always be appropriate. Treatment failure, whether due to lack of drug efficacy, patient non-compliance, or medication toxicities, is also a difficult issue. Fortunately, several new treatment approaches are now available or under development. Several of these are directed at urate lowering; others take an anti-inflammatory approach (Table 1).

Among new urate-lowering options the xanthine oxidase inhibitor febuxostat (Uloric), approved in 2009 in the US, is the best-established and most widely used. More recently, in 2010, the FDA approved pegloticase (Krystexxa) for urate lowering in a more select group of patients—those with treatment-failure gout. Humans and some other mammalian species lack the gene for uricase, the enzyme that converts uric acid to the more soluble allantoin. Pegloticase is a recombinant simian/porcine uricase, given intravenously, that rapidly lowers serum urate levels. The drug is pegylated to minimize immunogenicity but nonetheless has a high potential for infusion reactions, including anaphylaxis. In addition to its anaphylactic potential, pegloticase’s value is also limited by its expense as a biological agent, and by the fact that its efficacy may wane with time in some patients, presumably related to the development of auto-antibodies.

Despite these concerns, pegloticase offers a valuable new treatment option for patients with chronic, refractory gout, including those with tophi. Patients with tophi frequently have extensive urate deposits that impair serum urate lowering. Several studies and case reports suggest that pegloticase may be particularly effective for these patients. In one recent study presented by Baraf and colleagues at the 2010 ACR meeting, data from two 6-month double-blind control trials of pegloticase followed by an open label extension for up to 30 months was reanalyzed for the ability of pegloticase to reduce tophi. Pegloticase substantially reduced both the size and number of tophi; the total number of tophi across all patients declined from more than 300 to less than 150. These data suggest that pegloticase may be particularly useful for debulking MSU deposits. Whether such patients could then be maintained using less aggressive therapy remains to be determined.

Recent understanding of the importance of IL-1β in the genesis of crystal-driven inflammation has led investigators to evaluate anti-IL-1β therapy as an alternative to current anti-inflammatory gout treatments. Three such agents are under investigation, each with a slightly different mechanism of action. Anakinra, currently approved for treatment of rheumatoid arthritis, is a recombinant IL-1 receptor antagonist. Rilonacept is a genetic construct that bridges two IL-1 receptors through an immunoglobulin Fc backbone. Finally, canakinumab is a recombinant, humanized anti-IL-1β antibody. All three have the capacity to bind and neutralize either IL-1β itself or the IL-1 receptor.

Anakinra was the first of these agents to demonstrate efficacy in an open-label trial in 10 patients with acute gout. Subsequently, both rilonacept and canakinumab have been studied in a variety of clinical settings, for both acute and
chronic gout and as gout prophylaxis during urate-lowering therapy. Rilonacept has demonstrated efficacy in treating patients with chronic gouty arthritis. At the ACR 2010 annual meeting, Terkeltaub also reported on the efficacy of rilonacept in preventing acute attacks in patients starting allopurinol. Regular treatment with rilonacept resulted in fewer total flares, fewer flares per patient, and fewer flare days per patient compared to placebo.

Canakinumab demonstrated efficacy in treating acute flares of gout. In a phase II study, a single subcutaneous injection of canakinumab was at least as effective as 40 mg triamcinolone in relieving acute gout attacks. One particular advantage of canakinumab may be its long half-life: in the aforementioned study, use of a one-time dose of canakinumab not only abrogated the index attack but markedly reduced the recurrence of attacks for at least the next two months. This long duration may make canakinumab particularly useful as a prophylactic agent. Indeed, in an abstract presented at the 2010 ACR annual meeting, a single injection of canakinumab was more effective than colchicine 0.5 mg daily for prophylaxis against acute gouty attacks, with a duration of at least 16 weeks.

Identification of the URAT1 and GLUT9 transporters (discussed above) has also spurred drug development.

### Table 1 Summary of Medications Recently Approved or Under Active Investigation for Gout

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication (or treatment under investigated)</th>
<th>Availability</th>
<th>Mechanism</th>
<th>Target patients for use of drug</th>
</tr>
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<tbody>
<tr>
<td>Febuxostat (Uloric)</td>
<td>Urate lowering</td>
<td>FDA approved for gout; available</td>
<td>Xanthine oxidase inhibitor: reduces uric acid formation</td>
<td>Patients with allopurinol failure or intolerance; mild or moderate renal insufficiency</td>
</tr>
<tr>
<td>Pegloticase (Krystexxa)</td>
<td>Treatment failure gout</td>
<td>FDA approved for gout; available</td>
<td>Recombinant uricase: converts uric acid to allantoin, reducing sUA</td>
<td>Patients with chronic gout or high tophus burden, refractory to other ULT</td>
</tr>
<tr>
<td>RDEA594</td>
<td>Urate lowering, perhaps in combination with allopurinol</td>
<td>Under investigation</td>
<td>Inhibits URAT1 in the renal proximal tubule: blocks urate re-absorption</td>
<td>Patients with allopurinol failure or intolerance; possible alternative to probenecid</td>
</tr>
<tr>
<td>Tranilast</td>
<td>Urate lowering in combination with allopurinol (combination called NU1618)</td>
<td>Available in Japan as an anti-allergic agent; under investigation for gout in combination with allopurinol</td>
<td>Inhibits URAT1 and GLUT9a in the renal proximal tubule: blocks urate re-absorption</td>
<td>Patients with allopurinol failure; possible alternative to probenecid</td>
</tr>
<tr>
<td>Anakinra (Kineret)</td>
<td>Treatment of acute gout or possibly prophylaxis</td>
<td>FDA approved for rheumatoid arthritis; off-label use in gout</td>
<td>Recombinant IL-1Ra: binds to IL-1R1 and blocks IL-1β signaling</td>
<td>Patients with contraindications to or failure of NSAIDs, colchicine, or steroids</td>
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<tr>
<td>Rilonacept (Arcalyst, IL-1 Trap)</td>
<td>Symptoms of chronic gouty arthritis; prophylaxis during ULT</td>
<td>FDA approved for CAPS; under investigation in gout</td>
<td>Fusion protein comprised of extracellular domains of IL-1R1 and IL-1RaP, linked to Fc portion of IgG1; binds and blocks IL-1β</td>
<td>Patients with contraindications to or failure of NSAIDs, colchicine, or steroids</td>
</tr>
<tr>
<td>Canakinumab (Ilaris)</td>
<td>Treatment of acute gout or prophylaxis during ULT</td>
<td>FDA approved for CAPS; under investigation in gout</td>
<td>Human monoclonal antibody with IL-1β specificity: binds and blocks IL-1β</td>
<td>Patients with contraindications to or failure of NSAIDs, colchicine, or steroids</td>
</tr>
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</table>

CAPS: cryopyrin-associated periodic syndrome; IL-1R1: IL-1 receptor type I; IL-1Ra: IL-1 receptor antagonist; sUA: serum uric acid; ULT: urate lowering therapy.
RDEA594 is a URAT1 inhibitor that has shown efficacy for urate reduction compared to placebo in a phase II trial. Data from another phase II trial presented in abstract form at the EULAR 2011 meeting suggest that RDEA594 combined with allopurinol may offer added urate reduction compared to allopurinol alone. It appears that this agent may be efficacious even in the setting of mild or moderate renal insufficiency, which would be an advantage over probenecid. Tranilast, another novel urate lowering agent that inhibits URAT1 and GLUT9, has also been evaluated in phase II studies, used in combination with allopurinol for added serum urate reduction (combination product called NU1618).

Conclusion
For decades the overall pace of gout research had been slow, maintained largely by a handful of dedicated researchers. In contrast, the past decade has seen both a rise in gout prevalence and a resurgence in scientist and clinician interest. As our understanding of gout pathophysiology grows, it is likely that we will not only see the development of newer and better agents to treat gout, but also a better understanding of how to prevent its onset and its possible implications in cardiovascular, renal, and potentially other disease states.

Disclosure Statement
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