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New Agents for the Treatment of Gout and Hyperuricemia: Febuxostat, Puricase, and Beyond

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Abstract The rising prevalence of gout has led the pharmaceutical industry to rediscover what it had considered a forgotten disease. In April 2009, the Food and Drug Administration (FDA) approved febuxostat (Takeda Pharmaceuticals; Deerfield, IL), the first new urate-lowering gout drug in more than 40 years. In August 2009, the FDA approved colchicine for the treatment of acute gout. Several other pharmaceutical companies are also conducting clinical trials to test new drugs for acute and chronic gout. This article reviews new drugs and drugs in development in the management of acute and chronic gout.

Keywords Gout · Treatment · New agents

Introduction

In 1935, Hench et al. [1] published the following statement about the treatment of gout" "The classic treatment of gout by restriction of purine, hot or cold application, rest and preparations of colchicum … continues unchallenged. It has remained practically unchanged for years ... There has been no major change in the treatment of gout since the introduction of colchicum in the sixteenth century." Is this still true? The rising prevalence of gout has led the pharmaceutical industry to rediscover what it had considered a forgotten disease. The old drugs do not work well in some gout patients or are contraindicated in others due to multiple comorbidities commonly found in gout patients. Pharmaceutical companies are developing new drugs that may substitute the decades-old drugs for acute and chronic gout.

There are three types of treatment for gout: treating the acute attack; urate-lowering therapy; and, lastly, prophylaxis to prevent acute gouty attacks. In April 2009, the Food and Drug Administration (FDA) approved febuxostat (Takeda Pharmaceuticals; Deerfield, IL), the first new urate-lowering drug (ULD) in more than 40 years. Another new ULD, pegloticase (Savient Pharmaceuticals; East Brunswick, NJ), did not receive initial FDA approval, yet resubmission is expected in early 2010. In August 2009, the FDA approved colchicine for the treatment of acute gout. In addition, several other pharmaceutical companies are testing new drugs for acute and chronic gout in clinical studies. This article reviews new drugs and drugs in development for the management of acute and chronic gout.

New Agents and Agents in Development for the Treatment of Acute Gout and Prevention of Flares

Colchicine

Colchicine is an alkaloid derived from the autumn crocus, *Colchicum autumnale*. The precise mechanism by which colchicine relieves the intense pain of gout is not known. However, it is believed that the major relief of pain involves the major pharmacologic action of colchicine: binding to tubulin dimers [2]. It is also suspected to interfere with many leukocyte functions including diapedesis (ameboid movement), mobilization, lysosomal degranulation, and, most importantly, leukocyte chemotaxis. It is also believed to suppress monosodium urate (MSU) crystal-induced

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NALP3 inflammasome-driven caspase-1 activation and IL-1β processing [3].

Despite widespread use, oral colchicine did not have FDA approval until recently. It did not have FDA-approved prescribing information, dosage recommendations, or drug interaction warnings until August 2009. In the Acute Gout Flare Receiving Colchicine Evaluation (AGREE) trial [4•], a randomized, double-blind, placebo-controlled study in which 184 acute gout patients were treated for an acute attack within 12 h of the onset of the attack, low-dose colchicine (1.2 mg, then 0.6 mg 1 h later for a total of 1.8 mg) was found to be equally effective and better tolerated than high-dose colchicine (1.2 mg, then 0.6 mg hourly every 6 h for a total of 4.8 mg). For treatment of acute gout attacks in patients with mild (glomerular filtration rate [GFR], 50–80 mL/min) to moderate (GFR, 30–50 mL/min) kidney disease, adjustment of this recommended dose is not required.

There has been little information on colchicine drug–drug interactions until recently. Colchicine was found to be a substrate for both the CYP3A4 enzyme and P-glycoprotein (P-gp) transporter. Therefore, coadministration with drugs known to inhibit CYP3A4 and/or P-glycoprotein (P-gp) increases the risk of colchicine-induced toxic effects. These include cyclosporine, erythromycin, and calcium channel antagonists such as verapamil and diltiazem. Other examples of P-gp and strong CYP3A4 inhibitors include telithromycin, ketoconazole, itraconazole, HIV protease inhibitors, and nefazodone [5]. The FDA required patients treated with P-gp or strong CYP3A4 inhibitor drugs within 14 days of colchicine use for acute gout to have a dose reduction or interruption of colchicine treatment.

Further information for specific dosing recommendations and additional drug interaction information are found on the FDA website [6].

Interleukin 1β Inhibitors

Interleukin 1β (IL-1β) seems to have an important role in gouty inflammation. MSU crystals stimulate IL-1 release by monocytes and synovial mononuclear cells [7] as well as the cryopyrin (NLRP3) inflammasome, an intracellular, multiprotein complex. Cryopyrin regulates protease caspase-1 and controls the activation of IL-1β. Once caspase-1 becomes active and cleaves pro–IL-1β to release the mature p17 form of IL-1β resulting in the active IL-1β [3]. The release of IL-1β [3, 8] promotes neutrophil influx into the joint and inflammation.

IL-1β is an important cytokine involved in gouty inflammation and IL-1β blockade may be a novel approach to treat acute gout attacks. IL-1 inhibition has now been shown to have a beneficial effect in gouty inflammation. Anakinra, an IL-1 receptor antagonist, significantly relieved pain following acute gout in patients who could not tolerate or had failed standard anti-inflammatory therapies [9••]. So et al. [9••] studied the response to IL-1 receptor antagonist: 100 mg of daily subcutaneous administration of anakinra for 3 days in 10 patients with acute gout. They reported a 78% response in their pilot study of 10 patients [9••]. Subcutaneous administration once a week of rilonacept, another IL-1 inhibitor, decreased disease activity and pain in patients with chronic active gout [10]. Another IL-1 inhibitor currently in trials, canakinumab, a fully human monoclonal antihuman IL-1β antibody, binds to human IL-1β and thus blocks the interaction of this cytokine with its receptors. It does not bind IL-1α or IL-1 receptor antagonist (IL-1ra). Recently, canakinumab completed a phase 2 adaptive dose-ranging, multicenter, single-blind, double-dummy, active-controlled study to determine the target dose of canakinumab in the treatment of acute gout flares in patients who are refractory to or have a contraindication to nonsteroidal anti-inflammatory drugs (NSAIDs) and/or colchicine [11••]. Canakinumab (150 mg) was found to provide rapid pain relief. In this study, a statistically significant dose response was observed at 72 h for canakinumab (150 mg, administered subcutaneously). It was superior, starting at 24 h, in providing pain relief compared with 40 mg of triamcinolone acetonide given intramuscularly. The median time to 50% reduction in pain was reached at 1 day with canakinumab(150 mg) compared with 2 days for the triamcinolone acetonide group (P=0.0006) [11••].

In addition, rilonacept was studied as prophylactic therapy when initiating urate-lowering therapy (allopurinol) [12••]. This was a placebo-controlled study of rilonacept for gout flare prophylaxis during initiation of urate-lowering therapy. Eighty-three patients were randomized (placebo [n=42]; rilonacept [n=41]). Twenty-two percent (n=9) of the rilonacept group and 48% (n=20) of the placebo group (P=0.022) had acute gout flares. Thus, rilonacept significantly reduced the gout flares during initiation of urate-lowering therapy (Table 1).

New Agents and Agents in Development for the Treatment of Chronic Gout

Febuxostat

Febuxostat inhibits both isoforms of xanthine oxidase, the rate-limiting enzyme in the purine metabolism cascade. Once-daily 40-mg and 80-mg doses of febuxostat have recently been approved by the FDA for the treatment of hyperuricemia in patients with gout. Febuxostat is primarily metabolized by oxidation and glucuronidation in the liver. Approximately 50% of the administered febuxostat is

Table 1 Drugs in development for the treatment of acute gout and prophylaxis

Drug	Mechanism	Company	Status
Canakinumab	Fully human IL-1 monoclonal antibody	Novartis (Basel, Switzerland)	Phase 3 trial in gout to start
Rilonacept	IL-1 trap	Regeneron (Tarrytown, NY)	Phase 3 trial in gout to start

IL—interleukin

excreted in the urine but only 10% is excreted as unchanged drug or active metabolite [13]. This is in contrast to allopurinol, which is rapidly and extensively metabolized to oxypurinol, its active metabolite.

The pharmacokinetics of febuxostat are not significantly altered in patients with mild-to-moderate hepatic impairment [14]. In addition, mild-to-moderate renal impairment (chronic kidney disease [CKD] stages 2 and 3) seems to have little effect on the pharmacodynamics and pharmacokinetics of febuxostat [15]. These data suggest that febuxostat is currently the drug of choice in patients with CKD stages 2 and 3 in whom the safety of raising allopurinol doses to achieve a target serum urate (SU) of less than 6.0 mg/dL in these patients has not been studied. Further studies are needed to assess safety in patients with more advanced kidney disease (CKD stages 4 and 5).

The urate-lowering efficacy of febuxostat was defined in the febuxostat studies as the proportion of study patients with SU less than 6.0 mg/dL at the last study visit or at each of the last three study visits. Febuxostat, 40 mg daily, was found to have urate-lowering efficacy comparable to allopurinol (300 mg/d and 200 mg/d) [16], whereas febuxostat (80 mg/d and 120 mg/d) were found to be more effective than allopurinol (300 mg/d) in lowering SU to less than 6 mg/dL [17]. Extension 5-year studies found the efficacy of febuxostat to be sustained during long-term treatment and well tolerated compared with that of allopurinol [18]. After 5 years of febuxostat treatments, patients no longer endured gout flares. Tophi resolution was achieved in 69% of (18/26) patients with a baseline tophus, by the last study visit at 5 years [18].

Urate Oxidases or Uricases

Pegloticase

Urate oxidase (uricase) catalyses oxidation of uric acid into the more water soluble form allantoin. Allantoin is then excreted by the kidneys. The uricase protein is absent in humans because of gene mutations [19].

Rasburicase, a recombinant uricase, is FDA approved for pediatric patients who have leukemia, lymphoma, or solid tumor malignancies and are receiving chemotherapy that is expected to lead to tumor lysis syndrome [20]. Rasburicase was found to have good results in treating hyperuricemia in gout patients [21, 22]. However, its use is limited in patients with gout because it is highly immunogenic; has a short half-life (<24 h); and may cause anaphylaxis, hemolysis, and methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency.

Pegloticase was developed to treat gout patients who are refractory to current urate-lowering therapy (treatment failure gout). Two hundred and twelve patients were studied in two randomized, double-blind, placebo-controlled studies comparing pegloticase to placebo [23••]. All patients received intravenous infusions every 2 weeks. The patients were randomized to three treatment arms: pegloticase, 8 mg, at all infusions; pegloticase, 8 mg, and placebo infusions at alternate visits; or placebo infusions at all visits. The primary

Table 2 Drugs in development for the treatment of chronic gout

Drug	Mechanism	Company	Status
Pegloticase	Urate oxidase	Savient (East Brunswick, NJ)	Phase 3 completed; biologic license application for gout by FDA pending
Uricase-PEG 20	Urate oxidase	EnzymeRx (Paramus, NJ)	Phase 1 completed
Oxypurinol	Xanthine oxidase inhibitor (active metabolite of allopurinol)	Cardiome (Vancouver, British Columbia, Canada)	Phase 3 trial in gout initiated
Y-700	Xanthine oxidase inhibitor	Mitsubishi Tanabe Pharma Development America (Warren, NJ)	Phase 2
RDEA594	URAT1 inhibitor	Ardea (San Diego, CA)	Phase 2

FDA—US Food and Drug Administration

outcome of these studies was an SU less than 6.0 mg/dL for 80% of time during months 3 and 6 of the study. Persistent responders maintained SU less than 6.0 mg/dL for 6 months or more whereas transient responders had initial SU lowering, but SU returned to being greater than 6.0 mg/dL. SU levels normalized in 20% to 48% of patients ($P<0.001$ vs placebo). None of the placebo group patients responded. Forty-seven percent and 38% of patients given pegloticase every other week were responders (both $P<0.001$), as well as 20% and 48% of those given pegloticase every four weeks ($P=0.044$ and $P<0.001$) [23••]. Adverse events leading to treatment discontinuation were more common in the pegloticase-treated group (20% vs 2% with placebo; $P<0.05$) [23••]. Infusion reactions occurred in 26% of patients in the every-2-week treatment group; 40% of patients treated every 4 weeks; and 5% of the placebo group. These reactions were the most common reason for study withdrawal.

Anti-pegloticase antibodies were detected in most of the pegloticase-treated patients (88%). Surprisingly, they were also found in 15% of the placebo group. Development of anti-pegloticase antibodies is associated with loss of SU response and the majority of infusion reactions. Seventy-one percent of infusion reactions occurred in patients who had had an SU greater than 6 mg/dL. SU monitoring may predict antibody-mediated loss of response and a heightened infusion reaction risk during pegloticase therapy [24].

It is important to note that pegloticase treatment (8 mg every 2 wk) led to complete resolution of at least one tophus in 22% of patients within the first 3 months ($P=0.011$) and in 45% of patients within 6 months ($P=0.002$) of pegloticase treatment [25].

Uricase-PEG 20

Uricase-PEG 20 is another uricase in development [26]. In a phase 1 study of gout patients, uricase-PEG 20 given intramuscularly reduced SU in a dose-dependent manner. It was well tolerated and no antibodies were detected.

RDEA594

RDEA806, a pro-drug of RDEA594, is a URAT1 inhibitor responsible for its urate-lowering (uricosuric) effects. In a phase 1 study of more than 70 normal healthy volunteers, RDEA806 increased urinary excretion of uric acid in the first 24 h after dosing. Statistically significant decreases of 35% to 50% in SU levels were observed within 14 days. RDEA594 is currently in a phase 2, placebo-controlled, dose-response study to evaluate the safety and SU-lowering effects of 200, 400, and 600 mg of RDEA594 in 140 gout patients with hyperuricemia (SU ≥8 mg/d) after 4 weeks of treatment (Table 2) [27].

Conclusions

These are exciting times in the field of gout. Gout is no longer a forgotten disease. New agents for the treatment of acute and chronic gout have recently been approved by the FDA, and febuxostat and colchicine and pegloticase will be resubmitted to the FDA soon. In addition, several other pharmaceutical companies are conducting clinical studies testing new drugs for acute and chronic gout. We are headed to many changes in the treatment of gout. On the horizon are more treatment options for patients with gout who could not tolerate, have contraindications, or were not responsive to current treatment of acute and chronic gout.

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