COMMENTARY

A Look Down the Gout Treatment Pipeline

Allopurinol should, at least for now, remain the standard hyperuricemia treatment for gout, despite febuxostat's approval and the ongoing development of other gout pharmaceuticals.

The reason is that allopurinol – if adequately dosed – works for most patients. And after decades on the market, its safety profile is well known; it's also the least expensive option.

But even with adequate dosing, allopurinol does not work for everyone. For some, renal problems or previous hypersensitivity reactions make its use problematic.

That's where the newer options come in. For rheumatologists and patients alike, they mean that allopurinol is not the end of the line anymore.

Soon, there will likely be enough options to treat every gout patient.

We recently reviewed febuxostat, as well as pegloticase and other drugs in the gout pipeline (Lancet 2010 Aug. 17 [doi: 10.1016/S0140-6736(10)60665-4]). Our conclusion: Recent developments signal a new era in the treatment of gout.

Febuxostat (Uloric), approved by the Food and Drug Administration in February 2009, is already making a difference in clinical practice. It has been the experience of rheumatologists that patients who have had trouble with allopurinol often respond to febuxostat. The first dose can quickly drop urate levels down to 5 mg/dL or so, without side effects or rash. It's a great drug that is here to stay.

Like allopurinol, febuxostat is a xanthine oxidase inhibitor, but a more selective one that does not inhibit other enzymes in the purine and pyrimidine metabolic pathways.

Febuxostat dosing is easier, too. There are two options in the United States: 40 mg and 80 mg/day. The allopurinol dosing range is 100-800 mg/day, depending on patient's renal history and response.

Even with those advantages, febuxostat should be seen as a second-line agent, considered mainly for patients who are intolerant to allopurinol.

Febuxostat just has too many unknowns that are awaiting further information. For instance, it is not known if it is more effective than allopurinol. Febuxostat was better at dropping uric acid levels in trials, but it was compared with a suboptimal allopurinol dose (300 mg), and about 50% of gout patients need a higher dose to control hyperuricemia.

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Also, febuxostat's cardiac safety is a concern. Cardiac events were more common in febuxostat patients during trials, although the implications of that are not yet clear. Takeda Pharmaceutical Co., the drug's maker, is investigating the matter further.

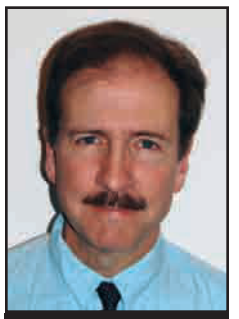
Finally, although no hypersensitivity reactions were attributed to febuxostat during trials, the FDA had received reports of 11 as of last May, including 2 anaphylactic reactions, 1 case of angioedema, and 2 of Stevens-Johnson syndrome.

Given the unknowns, clinicians need to use their judgment whether to push allopurinol to the therapeutic level rather than use febuxostat.

Patients with mild or moderate renal insufficiency might be an exception, however. Febuxostat dosage adjustments are not needed as long as patients' creatinine clearance is higher than 30 mL/min, according to the review article. Allopurinol is typically adjusted downward for diminished renal function.

Most people with renal insufficiency do fine even on allopurinol, as long as they are started on a low dose that is titrated upward to therapeutic effect, and are monitored for kidney function.

Febuxostat is making inroads in the United States: Some 139,565 prescriptions were written for it during its first 6 months on the market, according to health care market analytics firm SDI Health LLC.



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One should expect a more modest reception for the next gout treatment – pegloticase (Krystexxa) – that's likely to be approved by the FDA. The FDA's arthritis advisory committee recommended approval of the pegylated uricase in June 2009; the agency and pegloticase's manufacturer, Savient Pharmaceuticals Inc., appear to be working out the final manufacturing and prescribing details. Pegloticase's strength is rapid reduction of uric acid levels, to about 1 mg/dL within 24 hours in most cases.

Its market will be among patients who need that kind of power: those with severe tophaceous gout whose urate loads are so high that there is an urgent clinical need to lower it. Having a "big gun" for those situations would be a major advance, especially when allopurinol and febuxostat don't work or can't be used.

But pegloticase is destined to remain in the hands of subspecialists because it's tricky to use. The drug is a biologic that is administered intravenously a few times a month. In trials, at least 25% of patients developed antibodies to it, with subsequent infusion reactions, diminished effects, and treatment withdrawals, according to our review article.

Anaphylaxis developed in 7.3% of those who were infused every other week. The rapid uric acid reduction also led to frequent and sometimes severe gout flares.

Safe use is possible if rising concentrations of serum urate – a sign of antibody development and impending infusion reaction – are caught in time. But the use issues mean that pegloticase will have a limited audience. If approved, it is unlikely to be something that is used freely.

Other drugs intended for the management of gout are in early development. But, like febuxostat and pegloticase, they may help plug gaps in current therapy if they are approved for gout.

Already approved for cryopyrin-associated periodic syndromes, the anti-inflammatory interleukin-1 inhibitors rilonacept (Arcalyst) and canakinumab (Ilaris) are being studied both for acute gout and for prophylaxis. Conceivably, they could find a home among gout patients who have relative contraindications to steroids or cannot use colchicine or NSAIDs because they have heart failure, kidney disease, peptic ulcers, or some other problem.

The gout pipeline also contains the uricosuric RDEA594. It is thought to be more selective than probenecid and benzbromarone. However, findings from a small phase II trial show that RDEA594 was less effective than 300 mg of allopurinol in lowering serum urate. ■

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Study: Use of Statins May Limit Effect of Rituximab in RA

BY SHARON WORCESTER

FROM ANNALS OF THE RHEUMATIC DISEASES

Statins can inhibit the beneficial effects of rituximab on disease activity in rheumatoid arthritis patients, according to the findings of a study of 187 patients from the Dutch Rheumatoid Arthritis Monitoring registry.

After 6 months of treatment, the mean reduction in disease activity score using 28 joint counts (DAS28) was lower in 23 of 187 RA patients who were treated with both statins and rituximab (RTX) than in 164 patients treated with RTX alone (mean reduction of 0.5 vs. 1.0 point). The difference was of borderline statistical significance after adjustment for age, sex, baseline DAS28 score, and rheumatoid factor positivity, Dr. E.E.A. Arts of Radboud University Nijmegen (the Netherlands) Medical Center and colleagues reported.

Compared with the RTX-only patients, those exposed to statins also had a shorter effective period following RTX treatment (median of 7 months vs. 9 months), and were more likely to experience a failure event (hazard ratio, 2.3), after adjustment for the same confounders, the investigators said (Ann. Rheum. Dis. 2010 Oct. 18 [doi:10.1136/ard.2010.136093]).

All patients in the DREAM registry were included in the prospective cohort study, and all received 50 mg of prednisone with the first RTX infusion. Patients in both the RTX plus statin and the RTX-only groups had similar DAS28 scores at baseline.

The statin group was older (mean age, 66 vs. 58 years) and included a greater proportion of men than the RTX-only group (48% vs. 20%), but the groups were otherwise similar.

Although the study had a small sample size, it was sufficiently powered and showed a clinically relevant difference in DAS28 score changes over the 6-month study period, the investigators noted, adding that lack of randomization was another limitation of little concern, because "confounding by indication is unlikely."

More studies to replicate these findings and measure the magnitude of the effect are needed, they said.

"Significant interactions of statins with RTX in RA have not previously been shown. A critical review of common practice regarding concomitant use of statins in RTX-treated patients with RA is needed," they concluded. ■

VITALS

Major Finding: After 6 months of treatment, the mean reduction in disease activity score using 28 joint counts (DAS28) was lower in 23 of 187 RA patients who were treated with both statins and rituximab (RTX) than in 164 patients treated with RTX alone (mean reduction of 0.5 vs. 1.0 point).

Data Source: A prospective cohort study involving 187 patients from the DREAM registry.

Disclosures: The DREAM registry is funded by the Dutch affiliations of Wyeth Pharmaceuticals, Abbott Laboratories, Schering-Plough, Roche Pharmaceuticals, UCB Pharma, and Bristol-Myers Squibb.