Canakinumab Effective, Safe for Gouty Arthritis

BY MITCHEL L. ZOLER

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

LONDON – Use of canakinumab led to greater reductions in pain among patients with acute gouty arthritis flares after 3 days, and superior prevention of new flares during 12 weeks of follow-up, compared with triamcinolone acetonide in a pair of phase III trials that together enrolled 456 patients.

"Canakinumab is a potential new therapeutic option for acute flares in frequently flaring gouty arthritis patients with limited treatment options," Dr. Naomi Schlesinger said at the meeting.

VITALS

Major Finding: At 3 days after a single drug dose, gouty arthritis patients who were treated with canakinumab had a statistically significant, average reduction of 11 mm on their pain score, compared with patients who were treated with triamcinolone acetonide (on a 0- to 100-mm visual analog scale). After 12 weeks on randomized treatment, patients treated with canakinumab had a statistically significant 55%-68% relative decrease in new-flare frequency, compared with triamcinolone acetonide–treated patients.

Data Source: The Beta-RELIEVED and Beta-RELIEVED II trials, two identically designed studies that together randomized 456 patients with recent flares of gouty arthritis who were contraindicated for, intolerant of, or unresponsive to NSAIDs and colchicine to treatment with canakinumab or triamcinolone acetonide.

Disclosures: The beta-RELIEVED trials were sponsored by Novartis, which markets canakinumab (Ilaris). Dr. Schlesinger said that she is on the advisory board of Novartis, Enzyme Rx, Takeda, URL Pharma, and Savient. She is a consultant to and has received research grants from Novartis, and is on the speakers bureau of Takeda and Savient. Dr. So said that he is a consultant to Novartis, Bristol-Myers Squibb, Merck, Pfizer, and UCB Pharma. Dr. Khanna said that he is a consultant to Novartis, Takeda, Savient, and UCB Pharma.

Canakinumab is a fully human monoclonal antibody to interleukin (IL)-1 beta that selectively binds to and inhibits the proinflammatory molecule IL-1 beta, and already has Food and Drug Administration approval for treating CAPS (cryopyrin-associated periodic syndromes).

Based in part on the efficacy and safety data from the two reported phase III trials, Novartis, the company that markets canakinumab (Ilaris), filed an application with the FDA earlier this year for a supplemental indication for treating gouty arthritis flares. The FDA's Arthritis Advisory Committee discussed this application on June 21.

In the two new gouty arthritis trials, canakinumab's safety profile during the first 12 weeks of treatment "appeared consistent with longer-term safety data from CAPS patients; there were no safety signals related to specific organ class," said Dr. Schlesinger, chief of the division of rheumatology and connective tissue research at the Robert Wood Johnson Medical School in New Brunswick, N.J. The most notable safety observation she made from the new results centered on "a modest increase in infections, mostly mild to moderate, with no opportunistic infections reported," she said.

Despite this promising safety and efficacy, one expert viewed canakinumab as an agent for a "niche population, patients [with gout] who flare and you can't do anything about it" using standard drugs, commented Dr. Dinesh Khanna, a rheumatologist specializing in gout at the University of California, Los Angeles.

Goutologists see a lot of patients with diabetes, kidney disease, and hypertension who can't take NSAIDs or colchicine. "You also can't give them a steroid monthly, so these patients flare because of their high uric acid level and you're stuck. These are the patients who can be treated with an anti-IL-1 beta to prevent gout attacks," he said in an interview.

The Beta-RELIEVED (Response in Acute Flare and in Prevention of Episodes of Reflare in Gout) and Beta-RELIEVED II trials enrolled patients within 5 days of an acute flare of gouty arthritis who had at least three flares during the prior year and were contraindicated for, intolerant of, or unresponsive to NSAIDs and colchicine. All patients met the American College of Rheumatology's diagnostic criteria for gouty arthritis, and had pain intensity of at least 50 mm on a visual analog scale of 0-100 mm.

The researchers randomized patients to receive a subcutaneous injection of 150 mg canakinumab or an intramuscular injection of 40 mg triamcinolone acetonide. Patients who reflared during the subsequent 12 weeks during the first phase of the study qualified to receive an additional dose of their assigned drug with each flare.

One of the study's two primary end points was pain resolution at 72 hours after initial treatment. At that time, patients treated with canakinumab in the Beta-RELIEVED study had an average pain score that was 11 mm lower than that of patients in the comparator group, a statistically significant difference, reported Dr. Alexander So, a study coinvestigator and professor of rheumatology at the University of Lausanne (Switzerland).

Patients who were treated with canakinumab began to show significantly better pain reduction, compared with those who got triamcinolone within 12 hours after their first dose, and the advantage in pain relief continued each time the investigators measured pain during the first 7 days after treatment, Dr. So said. Neither Dr. So nor Dr. Schlesinger reported the results for this end point from the Beta-RELIEVED II trial.

The second primary end point was the percentage of patients having new flares during the first 12 weeks following their initial therapy. In the Beta-RELIEVED trial, 19% of the 115 patients who were treated with canakinumab and 37% of the 115 patients treated with triamcinolone had a new flare, a 55% relative risk reduction with canakinumab that was statistically significant. In the second trial, canakinumab use led to a 68% relative reduction in new flares, also a statistically significant difference in the study that randomized 226 patients, Dr. Schlesinger reported.

The canakinumab-treated patients also showed other signs of superior response in several secondary efficacy measures. Patients in the canakinumab group had a significant reduction in their mean number of flares, significantly less inflammation and swelling, and better suppression of inflammatory markers after 12 weeks, the researchers said.

In the safety analysis, canakinumab was associated with similar rates of all adverse events, a similar low rate of serious adverse events, and a similar low rate of adverse events leading to discontinuation, compared with patients who received triamcinolone. ■

As First-Line Gout Tx, Allopurinol Is Effective, Economical

BY MICHELE G. SULLIVAN

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE AMERICAN COLLEGE OF PHYSICIANS

SAN DIEGO – Allopurinol should remain the first-line agent for gout prophylaxis, despite competition from a newer drug, febuxostat, according to Dr. John Pendleton.

Allopurinol is very effective, can be safely titrated for those with renal impairment, and is the most cost-effective option, he said at the meeting.

"I still recommend allopurinol as the initial treatment, because you don't need a 24-hour urine collection to give it; it's effective in both overproducers and underexcretors [of uric acid]; it can be taken just once a day; and it's safe and effective for those with mild renal insufficiency when the dose is adjusted," said Dr. Pendleton, an internist in Roanoke, Va.

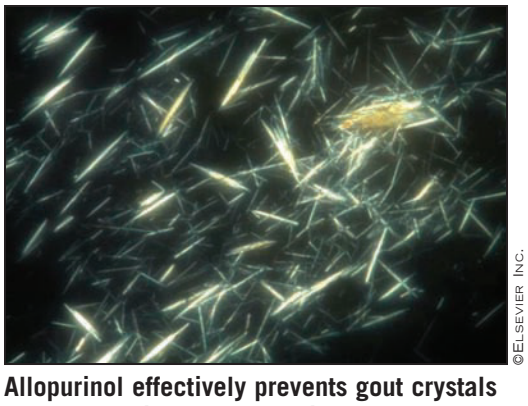
"Generic allopurinol costs about $15 per month. The brand name costs about $43 per month. But the price for febuxostat comes in at about $156 per month," he said.

With either drug, the goal is to lower uric acid levels to below 6 mg/dL, said Dr. Pendleton, referring to a retrospective study of 276 patients with recurrent gout attacks (Arthritis Rheum. 2004; 51:321-5).

In the study, "among the 81 patients with a uric acid of less than 6 mg/dL, 88% had no recurrent attacks during the 3-year observational period," he said.

Allopurinol has been the "standby drug" for gouty arthritis for 60 years, and still performs admirably, he noted. Most initial doses range from 50 to 300 mg/day, but "some recent studies suggest that only 25% of patients will reach the uric acid target on that regimen. For many patients, we need to increase the dose to get that level down."

The dose should be incrementally increased every 3-4 weeks to reach the uric acid target level; doses of up to 800 mg/day are approved for this indication. "But if you're not able to achieve this desired level by pushing the dose close to 800 mg, I would consider trying febuxostat."



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Allopurinol effectively prevents gout crystals (above) and is a cost-effective therapy.

Febuxostat, a xanthine oxidase inhibitor, is more selective and potent than allopurnol. "It's metabolized in the liver and very little of the active drug is excreted renally, raising the possibility that it might be safer in patients with mild to moderate renal insufficiency," Dr. Pendleton said.

It's not easy to fully compare the two, because all three of the studies on the basis of which febuxostat was approved used a fixed-dose allopurinol regimen. "None of them allowed the total upward titration of allopurinol for a fair comparison," Dr. Pendleton pointed out.

The studies concluded that 40 mg of febuxostat was as effective as 300 mg of allopurinol. "The higher dose [of febuxostat 80 mg] seemed to be more effective than 400 mg allopurinol, but again, the studies did not allow for an upward titration" of the comparator, he said.

Although none of the patients in those trials had a creatinine level of more than 2.5 mg/dL, "a short-term study suggests that febuxostat dosing would not need to be adjusted even with a very low creatinine clearance [of 10-29 mL/min]. But just the same I would be very careful in that setting," Dr. Pendleton said (Am. J. Ther. 2005;12:22-34).

Dr. Pendleton said he had no disclosures. ■