

Febuxostat Cut Uric Acid in Renal Impairment

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SAN DIEGO — Febuxostat was more effective than allopurinol for management of gout, even in patients with moderate renal impairment, according to data from a company-sponsored trial.

The 28-week trial, Febuxostat vs. Allopurinol and Placebo in Subjects With Hyperuricemia and Gout, known as APEX, revealed that 4 of 9 gout patients with moderate renal impairment (serum creatinine between 1.6 and 2 mg/dL) who received febuxostat at a dose of 80 mg/day achieved a serum urate level less than 6 mg/dL in their final three measurements, as did 5 of 11 patients who received 120 mg/day and 3 of 5 patients who received 240 mg/day.

None of the 10 patients with moderate renal impairment who received allopurinol, at 100 mg a day, achieved that goal,

Tophi of the hands decreased in size more significantly in patients on febuxostat than in those taking allopurinol for management of gout.

Dr. H. Ralph Schumacher said at the annual meeting of the American College of Rheumatology.

Phase III results from the company-sponsored trial on febuxostat for gout were first reported at last year's annual meeting of the

American College of Rheumatology. The presentation at the most recent ACR annual meeting included data on more patients as well as on those with renal impairment; the trial was shorter than the earlier investigation. Dr. Schumacher's new report included data on 1,067 patients with gout and a serum urate level greater than 8 mg/dL followed for 28 weeks. Last year's report was on 760 patients, followed for 52 weeks.

The new results were very similar to last year's. Febuxostat at a dose of 80 mg a day decreased serum urate levels below 6 mg/dL in the last three measurements in 48% of patients. A dose of 120 mg a day reduced the last three measurements below 6 mg/dL in 65% of patients, and 240 mg a day reduced the last three measurements below 6 mg/dL in 69%.

The patients without renal impairment who received allopurinol received a dose of 300 mg a day, and, in those patients, the allopurinol reduced the last three measurements below 6 mg/dL in 20% of the group. No such decrease occurred in patients on placebo.

Noting that the study's primary requirement that patients have all three of their final serum urate measurements below 6 mg/dL to be considered a success is a "rigorous and demanding end point," Dr. Schumacher also noted that 90% of the patients on febuxostat had at least one serum urate measurement below 6 mg/dL during the trial. That compared with 40% of those on allopurinol and none on placebo. Seventy-five percent of

the subjects on 240 mg a day of febuxostat got at least one serum urate measurement below 4 mg/dL.

Tophi of the hands and feet decreased in size in patients on either active treatment, but the change was more significant among patients taking febuxostat, said Dr. Schumacher, professor of medicine at the University of Pennsylvania, Philadelphia.

Types of adverse events were similar in the patients with and without moderate renal impairment; dose of febuxostat did

not have an effect on adverse events, Dr. Schumacher added.

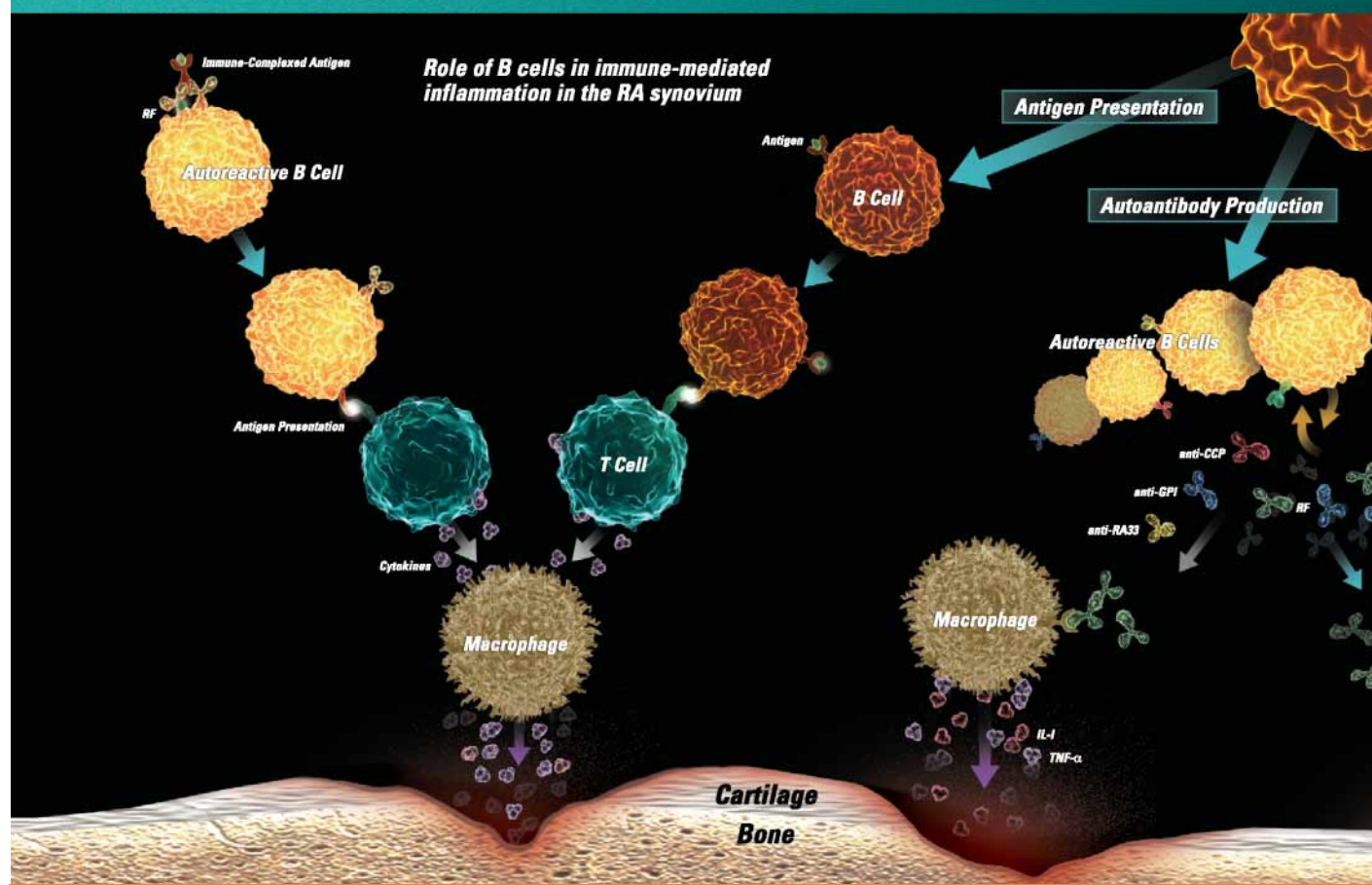
Gastrointestinal adverse events were most common and included diarrhea in 2%-4% of the patients on febuxostat and 7% of those on allopurinol.

Liver function abnormalities occurred in some patients and were deemed to be the result of colchicine use, used to manage gout flares and of little clinical concern, Dr. Schumacher said. Patients in all the groups had flares, particularly those on the

highest dose of febuxostat, though the flares decreased over time.

Serum creatinine levels did increase slightly with febuxostat treatment. But those levels did not increase to any greater degree in the patients with moderate renal impairment than they did in those without renal impairment, added Dr. Schumacher, who reported receiving funding from the company that makes febuxostat, TAP Pharmaceutical Products Inc., Lake Forest, Ill. ■

THREE CRITICAL ROLES OF B CELLS



Thirty years ago, B cells were considered a significant contributing factor in the pathophysiology of RA because of the disease's association with polyclonal B-cell activation and the presence of autoantibodies, such as rheumatoid factor (RF), and immune complexes in the joint.^{1,2} However, for much of the past 20 years, RA has mainly been considered as a T-cell mediated disease.¹ Only recently has new evidence rekindled strong interest in B cells and their important roles in the pathogenesis of RA.³

Current findings highlight 3 critical pathways by which B cells may initiate and perpetuate the inflammatory processes of RA: as highly efficient antigen-presenting cells,^{3,4} as producers of autoantibodies,⁵ and as producers of proinflammatory cytokines.^{3,4,6}

AS HIGHLY EFFICIENT ANTIGEN-PRESENTING CELLS, B CELLS MAY CONTRIBUTE SIGNIFICANTLY TO T-CELL RESPONSES IN RA.^{3,5,7-9}

- B cells may provide both signals needed to activate T cells^{3,4,7}
- RF-producing, autoreactive B cells may activate a wide range of T cells by presenting a variety of antigens to antigen-specific T cells⁸

B-cell-activated T cells produce proinflammatory cytokines that directly and indirectly perpetuate inflammation and joint destruction.⁹

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