

glucocorticoid-induced tumor necrosis factor receptor and messenger RNA expression levels of interleukin-10 and transforming growth factor  $\beta$  (often associated with regulatory T cells) did not differ between patient groups.

We have also measured the regulatory T-cell transcription factor FOXP3 by polymerase chain reaction in 100 samples of colorectal carcinoma and found no increase in either group of patients. Moreover, the median survival of patients with tumors that had high expression of FOXP3 (48 patients) or low expression of FOXP3 (50 patients) was 35.5 and 36.0 months, respectively ( $P=0.50$ ), and the median disease-free survival was 20 and 41 months, respectively ( $P=0.70$ ).

These data did not support an obvious correlation among subpopulations of regulatory T cells, VELIP1 status, and prognosis in colorectal cancer.

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## Febuxostat versus Allopurinol for Gout

**TO THE EDITOR:** The article by Becker et al. (Dec. 8 issue)<sup>1</sup> includes an inaccurate and misleading statement regarding the comparison of 80 mg per day of febuxostat with allopurinol for gout. The authors state that “the rates of discontinuation were similar in the 80-mg febuxostat and the allopurinol groups but were significantly higher in the 120-mg febuxostat group than in the other two groups ( $P=0.003$ ).”

The authors do not present a statistical analysis comparing the rates of discontinuation in the 80-mg febuxostat group with those in the allopurinol group. On the basis of the data they present, there was a significantly higher rate of discontinuation in the group receiving 80 mg per day of febuxostat ( $P=0.04$  by Fisher’s exact test).

This result affects the conclusions of the authors. A higher discontinuation rate in the group receiving 80 mg per day of febuxostat implies that febuxostat was not as well tolerated as allopurinol. Febuxostat may be an advance in the treatment of gout, but we need to be clear and precise in interpreting the trial data regarding its use.

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1. Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005;353:2450-61.

**TO THE EDITOR:** Given the incapacitating nature of acute attacks of gout and their substantial

prevalence in the United States,<sup>1</sup> the need to bring new, safer, and more effective agents to market is a priority. Moreover, clinicians regularly face the quandary that existing forms of therapy (including nonsteroidal antiinflammatory drugs, colchicine, and allopurinol) pose a risk of meaningful toxic effects,<sup>2,3</sup> especially among persons with the greatest need for treatment, such as the elderly and those with chronic renal insufficiency.

As such, the arrival of febuxostat is greatly anticipated. Its superior efficacy as compared with allopurinol in the reduction of serum urate concentrations, even to optimally low levels, is heralded in the *Journal*. Caution, however, needs to be exercised inasmuch as the reported frequency of adverse events leading to discontinuation of the drug occurred two and three times as often in the low-dose and high-dose febuxostat groups, respectively, as in the allopurinol group. Moreover, the occurrence of four deaths in the febuxostat groups, as compared with none in the allopurinol group, is further reason for pause. A compelling recent lesson regarding new arthritis medication is to be watchful as new agents are introduced into practice.<sup>4</sup> Vigilance and post-marketing pharmacoepidemiology can be particularly enlightening in this regard.

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**THE AUTHORS REPLY:** Our article contains an inaccuracy affecting interpretation of the study data. As identified by Dr. Lustberg, when Fisher's exact test is used to compare rates of discontinuation in the 80-mg febuxostat and allopurinol groups, a statistically significant difference ( $P=0.04$ ) between the two groups is found. Therefore, the statement regarding premature discontinuation should read, "The rates of discontinuation were significantly higher in both the 80-mg febuxostat group and the 120-mg febuxostat group than in the allopurinol group ( $P=0.04$  and  $P=0.002$ , respectively)." Corrections should be noted for similar text that appears in the Abstract and in the discussion of adverse events in the Results section of our article.

We reviewed the basis of these differences. Results reported in the article for comparisons of groups that were relevant to premature discontinuation were those determined with the use of a continuity-adjusted chi-square test ( $P=0.053$  for comparison of the allopurinol group with the 80-mg febuxostat group, and  $P=0.003$  for comparison of the allopurinol group with the 120-mg febuxostat group), rather than those determined with a Fisher's exact test, as intended.

All other analyses in the article have been re-

checked, and an additional point for correction has been identified. In Table 1 of the article, data about renal impairment are based on calculated creatinine clearance, and the P value should be 0.26, not 0.90. The P value of 0.90 was based on renal impairment as defined in the ineligibility criteria that were outlined in the Methods section. We believe that these changes do not affect the overall conclusion of the article, which is that febuxostat at a dose of 80 mg or 120 mg daily is more effective than allopurinol at a dose of 300 mg daily in lowering serum urate in patients with gout.

We thank Dr. Gelber for calling attention to the data in Figure 1 of the original article showing increased rates of premature discontinuation among patients treated with febuxostat. Although rashes and abnormal results of liver-function tests — the major adverse reactions leading to withdrawal — were mild to moderate in severity and reversible after discontinuation of febuxostat, we agree that roles for vigilance and post-marketing pharmacoepidemiology are essential in establishing the ultimate safety profile for febuxostat and, indeed, any new drug.

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## Hirsutism

**TO THE EDITOR:** Rosenfield (Dec. 15 issue)<sup>1</sup> states in his article on hirsutism that it is reasonable to forgo laboratory evaluation if hirsutism is mild and menses are regular and that routine testing for androgens other than testosterone is of little use. In addition, he states that testosterone arises also from androstenedione and dehydroepiandrosterone sulfate.

On the basis of our recent experience with more than 400 women who had been evaluated for hirsutism, we found that more than 80 percent fulfilled the diagnostic criteria for either adrenal enzyme deficiencies or the polycystic ovary syndrome. Since these conditions may necessi-

tate further follow-up, such as genetic testing or evaluation of glucose metabolism or for hypertension, laboratory studies are justified. In addition, there is evidence that testosterone derives from androstenedione and dehydroepiandrosterone (not the sulfated derivative),<sup>2</sup> both of which are weak androgens that have rarely been evaluated in the context of hirsutism.

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