ORIGINAL ARTICLE

Febuxostat Compared with Allopurinol in Patients with Hyperuricemia and Gout

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ABSTRACT

BACKGROUND

Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol for patients with hyperuricemia and gout.

METHODS

We randomly assigned 762 patients with gout and with serum urate concentrations of at least 8.0 mg per deciliter (480 μmol per liter) to receive either febuxostat (80 mg or 120 mg) or allopurinol (300 mg) once daily for 52 weeks; 760 received the study drug. Prophylaxis against gout flares with naproxen or colchicine was provided during weeks 1 through 8. The primary end point was a serum urate concentration of less than 6.0 mg per deciliter (360 μmol per liter) at the last three monthly measurements. The secondary end points included reduction in the incidence of gout flares and in tophus area.

RESULTS

The primary end point was reached in 53 percent of patients receiving 80 mg of febuxostat, 62 percent of those receiving 120 mg of febuxostat, and 21 percent of those receiving allopurinol ($P<0.001$ for the comparison of each febuxostat group with the allopurinol group). Although the incidence of gout flares diminished with continued treatment, the overall incidence during weeks 9 through 52 was similar in all groups: 64 percent of patients receiving 80 mg of febuxostat, 70 percent of those receiving 120 mg of febuxostat, and 64 percent of those receiving allopurinol ($P=0.99$ for 80 mg of febuxostat vs. allopurinol; $P=0.23$ for 120 mg of febuxostat vs. allopurinol). The median reduction in tophus area was 83 percent in patients receiving 80 mg of febuxostat and 66 percent in those receiving 120 mg of febuxostat, as compared with 50 percent in those receiving allopurinol ($P=0.08$ for 80 mg of febuxostat vs. allopurinol; $P=0.16$ for 120 mg of febuxostat vs. allopurinol). More patients in the high-dose febuxostat group than in the allopurinol group ($P=0.003$) or the low-dose febuxostat group discontinued the study. Four of the 507 patients in the two febuxostat groups (0.8 percent) and none of the 253 patients in the allopurinol group died; all deaths were from causes that the investigators (while still blinded to treatment) judged to be unrelated to the study drugs ($P=0.31$ for the comparison between the combined febuxostat groups and the allopurinol group).

CONCLUSIONS

Febuxostat, at a daily dose of 80 mg or 120 mg, was more effective than allopurinol at the commonly used fixed daily dose of 300 mg in lowering serum urate. Similar reductions in gout flares and tophus area occurred in all treatment groups.

HYPERURICEMIA, DEFINED AS A SERUM urate concentration exceeding the limit of solubility (about 6.8 mg per deciliter [400 μmol per liter]), is a common biochemical abnormality that reflects supersaturation of the extracellular fluid with urate and predisposes affected persons to gout. The clinical manifestations of gout (acute gouty arthritis, gouty arthropathy, chronic tophaceous gout, uric acid urolithiasis, and gouty nephropathy) result from deposition of monosodium urate or uric acid crystals from supersaturated body fluids.[1] The solubility of monosodium urate in extracellular fluids is influenced by a variety of factors, including pH, temperature, and sodium ion and protein concentrations[2-9]; under certain circumstances, urate solubility may be exceeded at concentrations of 6.0 mg per deciliter (360 μmol per liter) or lower.[3] Thus, a major goal in managing gout is long-term reduction of serum urate concentrations to clearly subsaturating levels; such reduction, if maintained over time, will prevent or reverse the formation and deposition of urate crystals.[10-12]

The most frequently used pharmacologic urate-lowering strategies involve reducing urate production with a xanthine oxidase inhibitor and enhancing urinary excretion of uric acid with a uricosuric agent. Urate-lowering agents are limited, however, in number, availability, and effectiveness.[13] Allopurinol, a xanthine oxidase inhibitor, is the most commonly prescribed of these agents. The average dose is 300 mg per day, although dosing recommendations range from 100 to 800 mg per day,[14-17] titrated to serum urate[15-17] and creatinine clearance. The side effects of allopurinol, although uncommon, may be severe or life-threatening and occur more often in patients with renal insufficiency.[14-17]

Febuxostat, a novel, orally administered, non–purine analogue inhibitor of xanthine oxidase, is being studied at daily doses of 80 and 120 mg for the management of hyperuricemia in patients with gout. Febuxostat is a potent xanthine oxidase inhibitor, has minimal effects on other enzymes involved in purine and pyrimidine metabolism,[18-22] and is metabolized mainly by glucuronide formation and oxidation in the liver.[23,24] In a study of subjects with renal impairment, the serum urate–lowering effect of febuxostat was unaltered.[25]

METHODS

PATIENTS

The Febuxostat versus Allopurinol Controlled Trial (FACT), a phase 3, randomized, double-blind, 52-week, multicenter trial, compared the safety and efficacy of febuxostat (taken orally once daily) with the safety and efficacy of allopurinol in adult subjects with gout and with serum urate concentrations of at least 8.0 mg per deciliter (480 μmol per liter). The subjects met the preliminary criteria of the American College of Rheumatology for acute arthritis of gout.[26] The ineligibility criteria included a serum creatinine concentration of more than 1.5 mg per deciliter (133 μmol per liter) or an estimated creatinine clearance rate of less than 50 ml per minute per 1.73 m^2 of body-surface area (because allopurinol was included in the study)[14,16]; pregnancy or lactation; use of urate-lowering agents, azathioprine, 6-mercaptopurine, thiazide diuretics, or medications containing aspirin (more than 325 mg daily) or other salicylates; a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 50; a history of xanthinuria, active liver disease, or hepatic dysfunction; use of prednisone at more than 10 mg per day; a change in hormone-replacement therapy or oral-contraceptive therapy within the previous three months; and a history of alcohol abuse or an alcohol intake of more than 14 drinks per week.

STUDY DESIGN

We conducted the study at 112 centers in the United States and Canada. Approval was obtained from institutional review boards or independent ethics committees. All subjects gave written informed consent and authorization according to the Health Insurance Portability and Accountability Act of 1996. Subjects already receiving urate-lowering therapy underwent a two-week washout period before undergoing randomization. A computer-generated central randomization schedule with a block size of three was used to assign each subject to one of three groups: febuxostat (Abbott Laboratories) at 80 mg per day, febuxostat at 120 mg per day, or allopurinol (Catalytica Pharmaceuticals) at 300 mg per day.

Initiation of therapy with urate-lowering agents is associated with an increased incidence of acute

gouty attacks[10,27,28]; accordingly, prophylaxis (250 mg of naproxen twice daily or 0.6 mg of colchicine once daily) was administered to all patients during the washout period and the first eight weeks of double-blind treatment. Subsequent flares of gout were treated at the investigators' discretion. At two weeks and four weeks, and monthly thereafter, each patient underwent a physical examination, vital signs were recorded, the serum urate concentration was measured, renal function was assessed, compliance with study drugs was assessed, laboratory tests were performed, and concomitant medication use, gout flares, and adverse events were recorded.

A treatment-emergent adverse event was defined as an adverse event occurring during the period between the first dose and 30 days after the final dose of the study drug. A serious adverse event was defined as an event that was life-threatening or that resulted in death, hospitalization or prolongation of hospitalization, persistent disability or incapacity, or a congenital anomaly or birth defect. A treatment-related adverse event was one considered by the investigator as possibly, probably, or definitely related to the study drug. In subjects with tophi, the area of one selected tophus was serially measured by the following method: two axes through the tophus at right angles to one another were identified, a pen was used to draw marks along the skin on the first axis from each side of the tophus until the nodule obstructed pen movement, the distance between the two pen marks over the top of the nodule was measured to the nearest millimeter, and the procedure was repeated along the second axis. The area of the tophus was then calculated by multiplying the two measurements.[29]

END POINTS

The primary efficacy end point was a serum urate concentration of less than 6.0 mg per deciliter at each of the last three monthly measurements. As prespecified, subjects who left the study before making at least three clinic visits were considered not to have reached the primary efficacy end point. The secondary efficacy end points included the proportion of subjects with serum urate levels of less than 6.0 mg per deciliter at each visit and the percentage reduction from baseline in the serum urate concentration at each visit. The clinical end points were the percentage reduction from baseline in tophus area, the change in the number of tophi at each visit, and the proportion of subjects requiring treatment for acute gout flares from weeks 9 through 52.

STATISTICAL ANALYSIS

For the primary efficacy end point, comparisions were made sequentially by a two-step closed-testing procedure: first, each febuxostat group was compared with the allopurinol group for noninferiority by using binomial confidence intervals for the difference between groups; second, each febuxostat group shown to be noninferior to the allopurinol group was tested for superiority to the allopurinol group by Fisher's exact test. Noninferiority to allopurinol was declared if the lower bound of the 97.5 percent confidence interval was greater than 10 percent. The overall 0.05 alpha level was maintained within each step by using binomial 97.5 percent confidence intervals for noninferiority tests and Hochberg's method for superiority tests.[30] Pairwise comparisons with the use of Fisher's exact test were also made between the proportions of patients in each treatment group who reached the primary efficacy end point within each of three groups defined by baseline urate concentration (less than 9.0 mg per deciliter [540 μmol per liter], at least 9.0 but less than 10.0 mg per deciliter [600 μmol per liter], and 10.0 mg per deciliter or more). Pairwise comparisons between groups for the secondary efficacy end points were made with the use of Fisher's exact test for the proportion of subjects with a serum urate concentration of less than 6.0 mg per deciliter and the proportion of subjects requiring treatment for a gout flare from weeks 9 through 52; analysis of variance was used to compare the percentage reduction from the baseline serum urate concentration; and the Wilcoxon rank-sum test was used to compare the percentage reduction from baseline tophus area and number of tophi. All reported P values are two-sided.

Post hoc analyses were also performed. Pairwise comparisons between groups were made with the use of Fisher's exact test for the proportions of subjects with serum urate concentration of less than 5.0 mg per deciliter (300 μmol per liter) and less than 4.0 mg per deciliter (240 μmol per liter). Fisher's exact test and the Wilcoxon rank-sum test, respectively, were used to compare the proportion of subjects requiring treatment for gout flares at weeks 49 through 52 and the percentage reduction from baseline tophus area at week 52 between subjects with average post-baseline serum urate con-

centrations less than 6.0 mg per deciliter and those with average concentrations of 6.0 mg or more per deciliter. No adjustments were made to the overall 0.05 alpha level for the secondary efficacy end points or post hoc analyses.

No interim analyses were performed. A sample of 750 subjects (250 per group) was targeted to provide 80 percent power to meet the noninferiority criteria and 90 percent power to detect a 15 percent difference between at least one febuxostat group and the allopurinol group for the primary end point, on the assumption of a true response rate of 60 percent for allopurinol[11,12,31-33] and at least 64 percent for febuxostat.

The study was designed by the academic investigators and the corporate sponsor (TAP Pharmaceutical Products). Representatives of TAP collected the data, and statisticians at TAP conducted all statistical analyses. All authors had access to the data and vouch for the veracity and completeness of the data and the data analysis. The manuscript was written in its entirety by the authors.

RESULTS

PATIENT CHARACTERISTICS

Of 1283 subjects screened, 762 were randomly assigned to treatment (Fig. 1). Of the 762 who underwent randomization, 760 received at least one dose of the study drug between July 2002 and February 2004: 256 received 80 mg of febuxostat, 251 received 120 mg of febuxostat, and 253 received 300 mg of allopurinol once daily. The mean age, sex ratio, racial distribution, mean baseline serum urate concentration, and history or presence of tophi were similar in the three groups (Table 1). The majority of the subjects were white men at least 50 years of age who reported that they drank alcohol. The subjects had had gout for an average of 12 years, 24 percent had tophi or a history of tophi, 16 percent had a history of urolithiasis, and 44 percent had previously taken allopurinol. Forty-four percent had hypertension, 34 percent had hyperlipidemia, 10 percent had artherosclerotic cardiovascular disease, and 62 percent were obese, defined as having a body-mass index of 30 or more. The mean baseline serum urate concentration ranged from 9.80 to 9.90 mg per deciliter (583 to 589 μmol per liter), with 41 percent of all subjects having a baseline serum urate concentration of at least 10.0 mg per deciliter (595 μmol per liter). Thirty-five percent of the subjects had mildly to moderately impaired renal function (Table 1). Compliance (determined by pill count) was similar in all groups (95.0 percent to 95.5 percent).

EFFICACY

Primary End Point

The primary efficacy end point — a serum urate concentration of less than 6.0 mg per deciliter at the last three measurements — was reached by 53 percent of the subjects taking 80 mg of febuxostat, 62 percent of those taking 120 mg of febuxostat, and 21 percent of those taking allopurinol ($P<0.001$ for each febuxostat group vs. the allopurinol group) (Table 2). At all ranges of initial urate levels tested, the primary end point was reached by higher proportions of febuxostat-treated subjects than allopurinol-treated subjects ($P<0.001$) (Table 2).

Secondary End Points

By week 2 of the study (the first visit after randomization), the proportion of subjects with serum urate concentrations of less than 6.0 mg per deciliter was significantly higher in the groups receiving febuxostat than in the group receiving allopurinol ($P<0.001$) (Table 2). These differences were sustained at all visits through week 52 ($P<0.001$). The mean percentage reduction from the baseline serum urate concentration at the final visit was also greater in both febuxostat groups than in the allopurinol group (Table 2). In addition, post hoc analysis showed that at week 52, the proportions of subjects with final serum urate concentrations of less than 5.0 or less than 4.0 mg per deciliter were significantly greater in both of the febuxostat groups than in the allopurinol group ($P<0.001$) (Table 2).

Gout Flares

During weeks 9 through 52, similar proportions of subjects in each group required treatment for at least one gout flare: 64 percent of those receiving 80 mg of febuxostat, 70 percent of those receiving 120 mg of febuxostat, and 64 percent of those receiving allopurinol. During the eight-week prophylaxis period, a significantly greater proportion of subjects receiving 120 mg of febuxostat required treatment for a gout flare than of those receiving 80 mg of febuxostat or those receiving allopurinol ($P<0.001$ for both comparisons) (Table 2). Withdrawal of prophylaxis was initially accompanied by a markedly increased incidence of gout flares in all

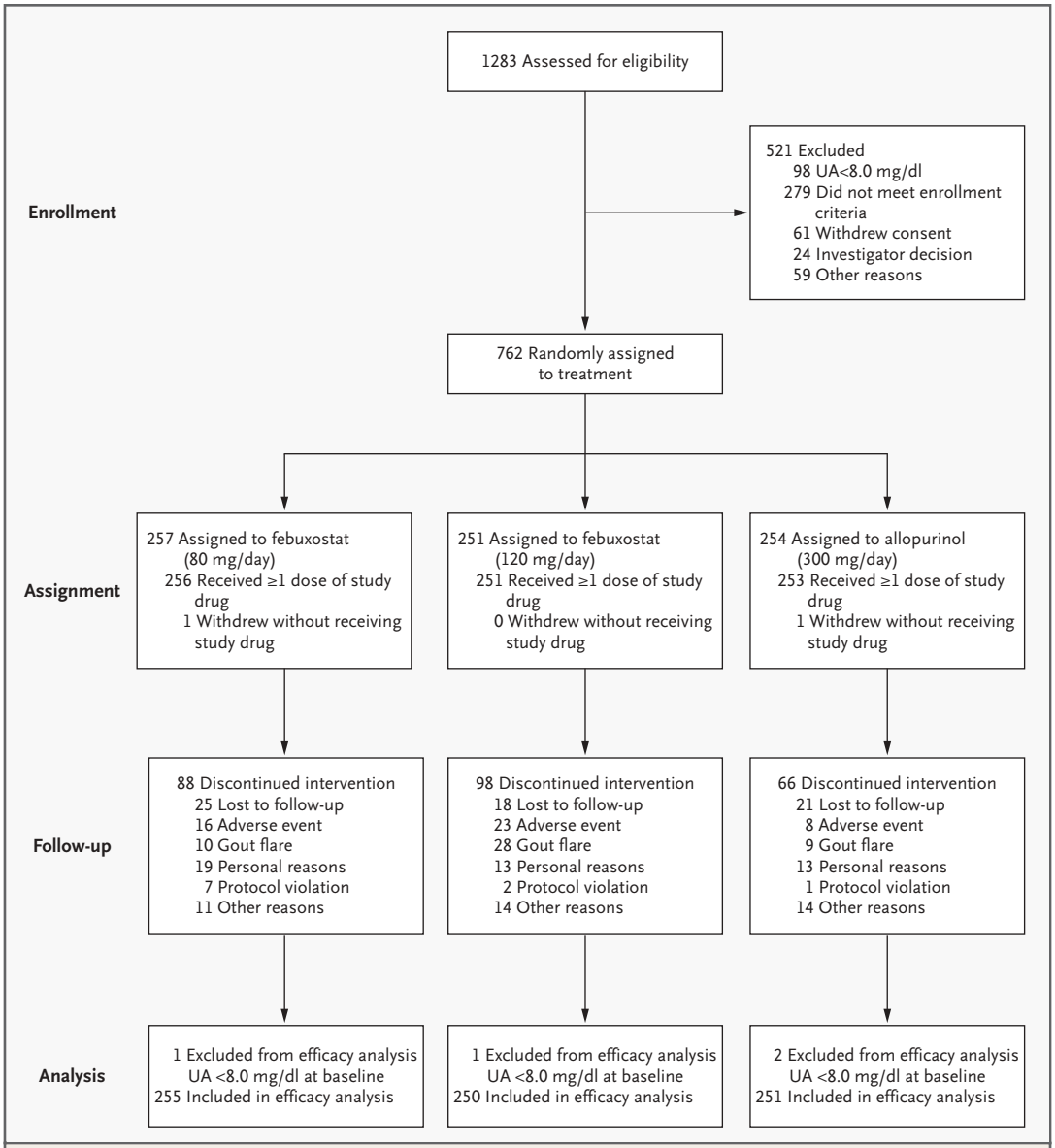

Figure 1. Flow of Participants through Each Stage of FACT.
UA denotes serum urate concentration.

groups (Fig. 2). The incidence of flare gradually decreased thereafter; by weeks 49 through 52, the final visit interval, the incidence was 8 percent among subjects receiving 80 mg of febuxostat, 6 percent among those receiving 120 mg of febuxostat, and 11 percent among those receiving allopurinol.

Tophi

The percentage reduction in tophus area was assessed in 156 subjects who had tophi at baseline. By week 52, the median percentage reduction in tophus area was 83 percent for subjects receiving 80 mg of febuxostat, 66 percent for those receiving 120 mg of febuxostat, and 50 percent for those receiving allopurinol. Little change in the number of tophi over time was noted in any of the treatment groups. There were no statistically significant differences among the groups in the percentage reduction in tophus area or in the reduction in the number of tophi (Table 2).

Table 1. Baseline Characteristics of the Subjects.*

Variable	Febuxostat, 80 mg/day (N=256)	Febuxostat, 120 mg/day (N=251)	Allopurinol, 300 mg/day (N=253)	All Subjects (N=760)	P Value†
Age — yr‡	51.8±11.7	52.0±12.1	51.6±12.6	51.8±12.1	0.95
Male sex — no. of patients (%)	243 (95)	243 (97)	243 (96)	729 (96)	0.56
Race — no. of patients (%)§					0.58
White	193 (75)	199 (79)	195 (77)	587 (77)	
Black	24 (9)	20 (8)	18 (7)	62 (8)	
Hispanic	22 (9)	17 (7)	19 (8)	58 (8)	
Asian	10 (4)	9 (4)	6 (2)	25 (3)	
Other	7 (3)	6 (2)	15 (6)	28 (4)	
Baseline serum urate concentration — mg/dl¶	9.80±1.24	9.84 ± 1.26	9.90 ± 1.23	9.84 ± 1.25	0.65
No. of years with gout	11.5±9.4	12.6 ± 9.9	11.6 ± 9.3	11.9 ± 9.6	0.38
History or presence of tophi — no. of patients (%)	59 (23)	65 (26)	62 (25)	186 (24)	0.76
Previous urate-lowering therapy — no. of patients (%)	112 (44)	106 (42)	113 (45)	331 (44)	0.86
Coexisting conditions — no. of patients (%)					
Body-mass index‖	32.7±6.1	32.3±5.7	32.6±6.1	32.5±6.0	0.74
Renal impairment**	90 (35)	98 (39)	81 (32)	269 (35)	0.90
Cardiovascular disease	23 (9)	28 (11)	23 (9)	74 (10)	0.65
Diabetes	17 (7)	17 (7)	19 (8)	53 (7)	0.92
Hypercholesterolemia	19 (7)	25 (10)	27 (11)	71 (9)	0.42
Hyperlipidemia	90 (35)	79 (31)	86 (34)	255 (34)	0.67
Hypertension	106 (41)	113 (45)	112 (44)	331 (44)	0.69
Obesity††	166 (65)	152 (61)	154 (61)	472 (62)	0.13
Urolithiasis	49 (19)	34 (14)	40 (16)	123 (16)	0.23
Use of low-dose aspirin‡‡	41 (16)	51 (20)	36 (14)	128 (17)	0.17
Metabolic syndrome§§	19 (7)	25 (10)	19 (8)	63 (8)	0.50
Tobacco use	43 (17)	43 (17)	45 (18)	131 (17)	0.96
Alcohol use	171 (67)	158 (63)	173 (68)	502 (66)	0.42

* Plus–minus values are means ±SD.
† P values were calculated by the chi-square test for categorical variables and by analysis of variance for continuous variables.
‡ Values are based on age at baseline.
§ Race was self-assigned.
¶ To convert values for serum urate to micromoles per liter, multiply by 59.48.
‖ The body-mass index is the weight in kilograms divided by the square of the height in meters.
** The criterion for renal impairment was a calculated creatinine clearance of less than 80 ml per minute per 1.73 m^2 of body-surface area, as estimated by the Cockcroft–Gault equation.[34]
†† Obesity is defined as a body-mass index of 30 or more.
‡‡ A user of low-dose aspirin was defined as a patient who was taking an ongoing total dose of 325 mg per day or less at completion of the study.
§§ The criteria for the metabolic syndrome were a serum triglyceride level of at least 150 mg per deciliter (1.7 mmol per liter), a blood pressure of at least 130/85 mm Hg, and a fasting serum glucose level of at least 110 mg per deciliter (6.1 mmol per liter).

Post Hoc Analyses

A post hoc analysis of the results of the trial was performed to test for differences in the reduction of gout flares and tophus area between subjects with a mean post-baseline serum urate concentration of less than 6.0 mg per deciliter and those with a concentration of 6.0 mg or more per deciliter. During weeks 49 through 52, the proportion of subjects requiring treatment for a gout flare was lower among subjects who reached a mean post-baseline serum urate concentration of less than 6.0 mg per deciliter than among those who did not (6 percent vs. 14 percent, P=0.005). The median reduction from baseline in tophus area at week 52 was 75 percent among subjects who reached an average post-baseline serum urate concentration of less than

Table 2. Primary and Secondary End Points.*

End Point	Febuxostat, 80 mg/day	Febuxostat, 120 mg/day	Allopurinol, 300 mg/day
Primary end point			
Serum urate <6.0 mg/dl at last 3 monthly visits†			
No./total no. (%)	136/255 (53)	154/250 (62)	53/251 (21)
Difference in proportions, 80-mg febuxostat vs. allopurinol — % (97.5% CI)‡	32 (23.1–41.3)		
P value§			<0.001
Difference in proportions, 120-mg febuxostat vs. allopurinol — % (97.5% CI)‡		41 (31.5–49.5)	
P value§			<0.001
Secondary end points			
Serum urate <6.0 mg/dl at final visit			
No./total no. (%)	185/249 (74)	193/242 (80)	88/242 (36)
P value	<0.001¶	<0.001¶	
Percent change in serum urate concentration from baseline at final visit			
Mean ±SD	−44.73±19.10	−51.52±19.91	−32.99±15.33
P value	<0.001,¶ <0.001‖	<0.001¶	
Serum urate <6.0 mg/dl at last 3 visits, according to baseline concentration			
Baseline <9.0 mg/dl			
No./total no. (%)	43/75 (57)	50/69 (72)	25/63 (40)
P value	0.04¶	0.001¶	
Baseline 9.0 to <10.0 mg/dl			
No./total no. (%)	44/75 (59)	60/81 (74)	19/80 (24)
P value	<0.001¶	<0.001¶	
Baseline ≥10.0 mg/dl			
No./total no. (%)	49/105 (47)	44/100 (44)	9/108 (8)
P value	<0.001¶	<0.001¶	
Serum urate <6.0 mg/dl			
Wk 2			
No./total no. (%)	196/245 (80)	211/241 (88)	98/235 (42)
P value	<0.001,¶ 0.03‖	<0.001¶	
Wk 52			
No./total no. (%)	129/159 (81)	119/145 (82)	70/178 (39)
P value	<0.001¶	<0.001¶	

6.0 mg per deciliter, as compared with 50 percent among those who did not (P=0.06).

ADVERSE EVENTS

The incidence of adverse events was similar in the three treatment groups (Table 3). Treatment-related adverse events included abnormal liver-function test results, diarrhea, headaches, joint-related signs and symptoms, and musculoskeletal and connective-tissue signs and symptoms. Most adverse events were mild to moderate in severity. The incidence of serious adverse events was similar in all groups; serious adverse events occurred in 51 subjects, 34 of whom continued in the study while the event resolved without recurrence. Four of the 507 patients in the two groups receiving febuxostat (0.8 percent) and none of the 253 in the allopurinol group died; all deaths were judged by the investigators to be unrelated to the study drugs. The difference between the numbers of deaths in the febuxostat groups

Table 2. (Continued.)

End Point	Febuxostat, 80 mg/day	Febuxostat, 120 mg/day	Allopurinol, 300 mg/day
Incidence of gout flares			
Day 1–wk 8 (prophylaxis)			
No./total no. (%)	55/255 (22)	90/250 (36)	52/251 (21)
P value	<0.001‖	<0.001¶	
Wk 9–52			
No./total no. (%)	147/228 (64)	150/215 (70)	150/234 (64)
Wk 49–52			
No./total no. (%)	13/167 (8)	9/153 (6)	20/185 (11)
Tophus change from baseline at wk 52			
No. of patients (median % change in area)	32 (–83)	26 (–66)	30 (–50)
No. of patients (median change in no. of tophi/patient)	33 (0)	28 (–1)	35 (0)
Post hoc analysis of serum urate at final visit			
<5.0 mg/dl			
No./total no. (%)	118/249 (47)	160/242 (66)	31/242 (13)
P value	<0.001,¶ <0.001‖	<0.001¶	
<4.0 mg/dl			
No./total no. (%)	50/249 (20)	100/242 (41)	4/242 (2)
P value	<0.001,¶ < 0.001‖	<0.001¶	

* Four subjects (one receiving 80 mg of febuxostat, one receiving 120 mg of febuxostat, and two receiving allopurinol) were excluded, as prespecified, from the efficacy analysis because their baseline serum urate concentration on day 2 was less than 8.0 mg per deciliter.
† To convert values for serum urate to micromoles per liter, multiply by 59.48.
‡ The 97.5 percent confidence interval (CI) based on the normal approximation for the binomial distribution is given.
§ P values were calculated by Fisher's exact test. An overall alpha level of 0.05 was maintained within each step by using Hochberg's method for superiority[30] and a binomial 97.5 percent confidence interval for noninferiority.
¶ The difference was statistically significant for the comparison with allopurinol.
‖ The difference was statistically significant for the comparison with 120 mg per day of febuxostat.

and the allopurinol group was not statistically significant (P=0.31). There were two deaths in the group receiving 80 mg of febuxostat: one from congestive heart failure and respiratory failure in a 65-year-old man, and one from retroperitoneal bleeding ascribed to anticoagulation therapy in a 77-year-old man. Two deaths occurred in the group receiving 120 mg of febuxostat: one from metastatic colon cancer in a 74-year-old man, and one from cardiac arrest in a 68-year-old man.

Eighty-eight subjects in the 80-mg febuxostat group, 98 in the 120-mg febuxostat group, and 66 in the allopurinol group discontinued the study (P=0.003 for the comparison between the 120-mg febuxostat and the allopurinol groups) (Fig. 1). The most frequent reasons for discontinuation were lost to follow-up, adverse events, and gout flares. The most common adverse event leading to withdrawal was abnormal liver-function test results, which accounted for the withdrawal of five patients receiving 80 mg of febuxostat, seven receiving 120 mg of febuxostat, and one receiving allopurinol (P=0.04 for the comparison between the 120-mg febuxostat and the allopurinol groups). Four subjects receiving 80 mg of febuxostat, four receiving 120 mg of febuxostat, and one receiving allopurinol discontinued the study because of rashes. Most of these were localized and transient maculopapular rashes that occurred during prophylactic treatment with either colchicine or naproxen and resolved after topical treatment.

DISCUSSION

This large, randomized, controlled clinical trial, conducted in subjects with hyperuricemia and gout, compared treatment with febuxostat and allopurinol with regard to safety, urate-lowering efficacy,

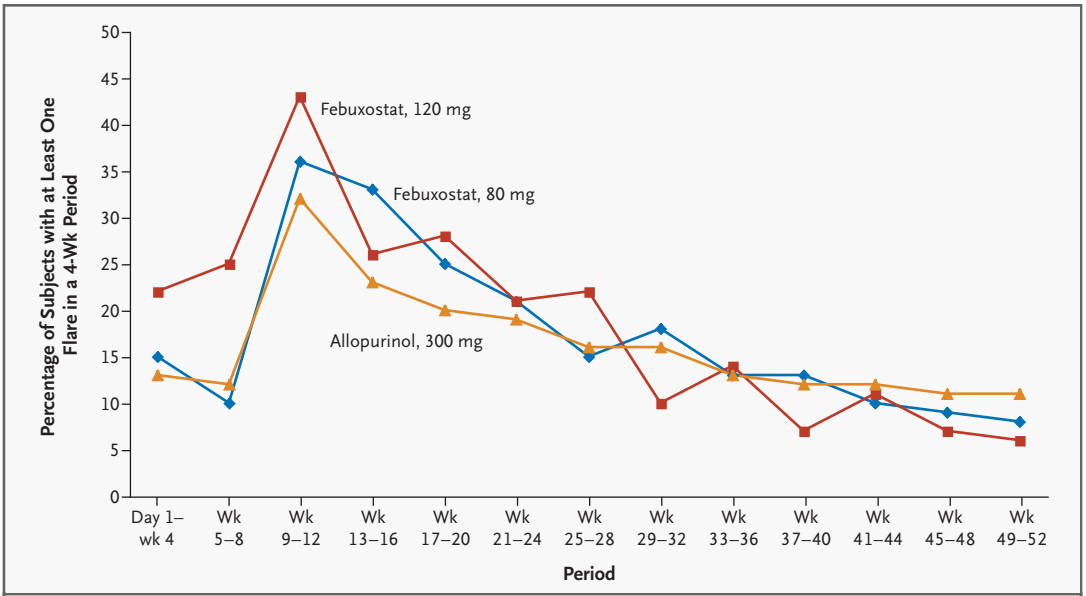

Figure 2. Subjects Requiring Treatment for Gout Flares.

The percentage of subjects in each interval is calculated by dividing the number of subjects with at least one gout flare in that interval by the number of subjects exposed to at least one dose of drug in that interval. Subjects may be counted in more than one interval. The subjects received prophylaxis during the period from day 1 to week 8. The results for the 80-mg febuxostat group are shown in blue, those for the 120-mg febuxostat group in pink, and those for the allopurinol group in yellow.

incidence of gout flares, and changes in tophus area. Administration of febuxostat or allopurinol resulted in prompt (within two weeks) and persistent reduction in serum urate concentration; however, all urate-lowering end points requiring serum urate concentrations of less than 6.0 mg per deciliter were reached by significantly greater proportions of subjects receiving daily febuxostat (80 or 120 mg) than subjects receiving allopurinol (300 mg). The clinical outcomes (reduction in gout flares and in tophus area) were not different in the febuxostat and allopurinol groups.

In this trial, the overall incidences of treatment-related adverse events were similar for all treatment groups, and most were mild to moderate in severity. 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 higher rate of discontinuation in the 120-mg febuxostat group was due to the higher incidence of gout flares and adverse events in this group. No serious rashes or hypersensitivity reactions occurred in this study. There were four deaths in the febuxostat groups and none in the allopurinol group; the difference between the febuxostat and the allopurinol groups was not statistically significant ($P=0.31$). Long-term studies are ongoing to provide further evaluation of the safety profile of febuxostat.

The high rate of gout flares in all groups during prophylaxis, and especially after withdrawal of prophylaxis, calls attention to a well-described[24,28,33] paradox with important implications for successful management of gout: the risk of acute gout flares is increased early in the course of urate-lowering treatment. This study clearly documents a role for more sustained prophylaxis during the initiation of urate-lowering therapy than was provided here.

Our study was designed to test the hypothesis that febuxostat is not inferior to allopurinol with respect to urate-lowering efficacy. On the basis of published studies,[11,12,31-33] we predicted that the primary end point (a serum urate concentration of less than 6.0 mg per deciliter) would be reached by 50 percent to 60 percent of the subjects receiving allopurinol at a dose of 300 mg per day. In fact, only 21 percent reached this end point. Two factors might contribute to the lower-than-expected urate-lowering efficacy of allopurinol. First, study entry required a baseline serum urate concentration of at

Table 3. Summary of Adverse Events.

Adverse Event	Febuxostat, 80 mg/day (N=256)	Febuxostat, 120 mg/day (N=251)	Allopurinol, 300 mg/day (N=253)
	no. of patients (%)		
Any treatment-emergent event*	205 (80)	189 (75)†	215 (85)
Any serious adverse event‡§	11 (4)	21 (8)	19 (8)
Any treatment-related adverse event§¶	63 (25)	60 (24)	57 (23)
Most frequent treatment-related adverse events‖			
Liver-function test abnormalities	9 (4)	13 (5)	11 (4)
Diarrhea	8 (3)	7 (3)	8 (3)
Headaches	3 (1)	4 (2)	8 (3)
Joint-related signs and symptoms (arthralgia, joint stiffness or swelling)	2 (<1)	6 (2)	6 (2)
Musculoskeletal and connective-tissue signs and symptoms (back, chest-wall, flank, or extremity pain and musculoskeletal stiffness)	5 (2)	3 (1)	5 (2)
Gastrointestinal atonic and hypomotility disorders (constipation, gastro-esophageal reflux disease)	5 (2)	2 (<1)	4 (2)
Nausea and vomiting symptoms	5 (2)	3 (1)	3 (1)
Neurologic signs and symptoms (dizziness, dysgeusia)	5 (2)	3 (1)	1 (<1)
Asthenic conditions (asthenia, fatigue)	4 (2)	2 (<1)	2 (<1)
Gastrointestinal signs and symptoms (epigastric and stomach discomfort)	5 (2)	1 (<1)	1 (<1)
Erythema (erythematous rash)	1 (<1)	1 (<1)	4 (2)
Peripheral edema	4 (2)	1 (<1)	1 (<1)

* A treatment-emergent event was an adverse event that occurred during the period from the first dose to 30 days after the final dose of the study drug.
† The difference from the allopurinol group was significant (P=0.01) by Fisher's exact test.
‡ A serious adverse event was life-threatening or resulted in death, hospitalization or prolongation of hospitalization, persistent or significant disability or incapacity, or congenital anomaly or birth defect. All of these events were considered by the investigator to be not related or unlikely to be related to the study drug.
§ There were no statistically significant differences among the groups.
¶ A treatment-related adverse event was considered by the investigator to be possibly, probably, or definitely related to the study drug.
‖ Adverse events were classified according to the definitions in the *Medical Dictionary for Regulatory Activities* (MedDRA)[35] on the basis of the signs and symptoms reported by the investigators. The most frequent treatment-related adverse events were defined as those reported for at least 2 percent of the subjects in at least one of the treatment groups.

least 8.0 mg per deciliter, and the mean baseline serum urate concentration was nearly 10.0 mg per deciliter, a level exceeded by 41 percent of the subjects. These baseline levels may not be uncommon in the current population of patients with gout,[12] but they exceed those reported several decades ago, when allopurinol was introduced.[36,37] Second, in order to confirm the persistence of the urate-lowering effect, the primary end point was defined as three successive measurements of serum urate of less than 6.0 mg per deciliter. It is likely that allopurinol would have been more effective at lowering urate levels if the dose had been titrated as recommended in the allopurinol package insert. In this trial, however, titration of allopurinol would have compromised the blinding of the study. Furthermore, no clinical trials have been conducted to assess the safety and efficacy of titration of the dose of allopurinol according to serum urate levels.

In retrospective, nonrandomized studies and in small, prospective studies, attainment and maintenance of serum urate concentrations of less than 6.0 mg per deciliter have been associated with long-term benefits in patients with gout, including reduction in the frequency of gout flares and decrease in the size or number of tophi.[10-12] In this study, reductions in the incidence of gout flares and in tophus area (the clinical end points) were also observed over time and were similar in all treatment groups. However, the current study was only 52 weeks in duration, and post hoc analysis of the relation between the incidence of gout flares and

an average post-baseline serum urate concentration of less than 6.0 mg per deciliter or 6.0 mg or more per deciliter found a significant difference only in the last 4 weeks. This suggests that a longer trial would be necessary to distinguish between urate-lowering agents with regard to superiority in clinical outcome.

The results of this study provide information generally applicable to the management of hyperuricemia in patients with gout. First, sustained lowering of serum urate was accompanied over months by a reduction in the incidence of gout flares and in tophus area, confirming the beneficial effects of sustained urate reduction on both the acute and the chronic manifestations of gout. Second, the greater reduction in gout flares and tophus area over time when the serum urate concentration is maintained at less than 6.0 mg per deciliter supports the use of the subsaturating range of less than 6.0 mg per deciliter as an appropriate target for the management of symptomatic hyperuricemia.

Dr. Becker, Dr. Schumacher, and Dr. Wortmann report serving as consultants for TAP Pharmaceutical Products. Dr. Joseph-Ridge, Ms. MacDonald, Ms. Eustace, Ms. Streit, and Mr. Palo are employees of TAP Pharmaceutical Products.

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APPENDIX

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CORRECTION

Febuxostat versus Allopurinol for Gout

To the Editor: The article by Becker et al. (Dec. 8 issue)[1] 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;353:2450-2461.

To the Editor: Given the incapacitating nature of acute attacks of gout and their substantial prevalence in the United States,[1] 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,[2,3] 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.[4] 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 rechecked, 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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