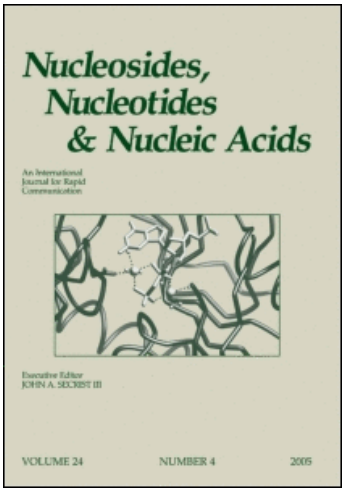

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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To cite this Article Becker, Michael A. , MacDonald, Patricia A. , Hunt, Barbara J. , Lademacher, Christopher and Joseph-Ridge, Nancy(2008) 'Determinants of the Clinical Outcomes of Gout During the First Year of Urate-Lowering Therapy', Nucleosides, Nucleotides and Nucleic Acids, 27: 6, 585 — 591
To link to this Article: DOI: 10.1080/15257770802136032
URL: http://dx.doi.org/10.1080/15257770802136032

Nucleosides, Nucleotides, and Nucleic Acids, 27:585–591, 2008

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770802136032

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DETERMINANTS OF THE CLINICAL OUTCOMES OF GOUT DURING THE FIRST YEAR OF URATE-LOWERING THERAPY

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□ *Clinical benefit early in urate-lowering treatment of gout is difficult to document. We examined data from 1,832 gouty subjects treated with either urate-lowering agents or placebo to identify determinants of gout flare incidence and tophus size during year 1 of treatment. Reductions from pretreatment serum urate levels influenced flare frequency and tophus size, but the effect of urate level on flare incidence was biphasic. Lower urate levels were associated with higher flare incidence early in treatment but lower incidence by one year. The complex relationship between urate-lowering and clinical outcome early in treatment has implications for both clinical and investigative approaches to urate-lowering management.*

Keywords Gout; hyperuricemia; serum urate; urate-lowering agents; tophi

INTRODUCTION

Hyperuricemia, defined as a urate concentration exceeding the limit of urate solubility in serum (approximately 6.8 mg/dL or 400uM) is a cardinal feature of patients with gout. Among individuals with asymptomatic hyperuricemia, the risk for development of clinical gout increases with increasing serum urate levels.[1] For management of repeatedly or chronically symptomatic gout, reversal of hyperuricemia and long-term maintenance of subsaturating serum urate levels (such as <6.0 mg/dL) are usually recommended.[2–5] Considerable evidence supports the view that persistent urate-lowering reduces the incidence and, ultimately, the severity of clinical gout, as reflected by reductions in the frequency of acute gout flares, in the size and number of palpable tophi, and in the numbers of crystals in joint fluid.[2–4,6] For example, the proportion of patients suffering recurrent gout flare in the second and third year of urate-lowering

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treatment was markedly lower among patients with average serum urate levels <6.0 mg/dL during the treatment period than in patients with serum urate levels averaging ≥7.0 mg dL.[3] In another study,[4] the velocity of gouty tophus size reduction was inversely related to serum urate level achieved during urate-lowering therapy.

An impediment to successful management of gout, however, is an increased risk for flares of gouty arthritis in the first weeks and months after initiation of urate-lowering therapy. This clinical worsening has been documented to occur independent of the means of urate-lowering employed,[2,3,5–10] so that acute flares in this setting are believed to result from changes in urate concentrations. The most tenable hypotheses to explain this paradox emphasize disruption by urate-lowering of a stable physical and/or chemical state of pre-existing urate crystal deposits. The mechanisms involved remain to be defined, but there is compelling evidence that successful prophylaxis of acute inflammatory attacks during initiation of urate-lowering can be accomplished with oral daily colchicine administration.[10] Nevertheless,repeated acute attacks in the early months of urate-lowering treatment may contribute to suboptimal patient adherence to urate-lowering agents such as allopurinol, to which <40% of patients were deemed compliant during a 2 year period of treatment monitoring.[11]

We reasoned that a clearer understanding of influences on clinical outcomes early in the course of urate-lowering for gout might benefit both therapeutic and investigative approaches to urate-lowering management. Thus, we examined data gathered in two large clinical studies of gouty subjects[2,8] treated with either allopurinol, febuxostat, or placebo in order to identify determinants of gout flare incidence and tophus size during the first year of urate-lowering treatment.

SUBJECTS AND METHODS

A total of 1,832 subjects with gout and baseline serum urate levels ≥8.0 mg/dL participated in one of two prospective, randomized, double-blind trials: either a 52-week study comparing daily allopurinol and febuxostat administration (N = 760 subjects);[2]or a 28-week trial comparing these urate-lowering agents with each other and with placebo (N = 1072 subjects).[8]Demographic characteristics and comorbidities among subjects randomized to the different study groups did not differ significantly and results of efficacy and safety analyses have been described in detail elsewhere.[2,8]

All subjects received prophylaxis with colchicine (0.6 mg, once daily) or naproxen (250 mg, twice daily) for the first 8 weeks of the trials. Serum urate level, the incidence of acute gout flares requiring treatment, and the size of index tophi[12] were measured at least monthly. For the

retrospective analyses discussed here, subjects were grouped by average post-baseline serum urate achieved regardless of the specific study agent or dose administered.

A multivariate logistic regression model was used to identify potential determinants of gout flare incidence. The model for gout flares during each four-week interval of the treatment period considered effects of the following: treatment group; baseline serum urate level; average post-baseline serum urate level; average percent change from baseline serum urate level; and the presence or absence of tophi at baseline. A linear regression model was used to identify potential determinants of changes in tophus size. The model for change in size of tophi during each four-week interval of the treatment period considered effects of the following: treatment group; average post-baseline serum urate level; primary tophus location (wrist/hand; ankle/foot/toe/instep; elbow; knee; or other); and baseline primary tophus size.

RESULTS

The urate-lowering effects of allopurinol and febuxostat were prompt, durable, and significant. Post-baseline serum urate levels were achieved within the first month of treatment and remained stable throughout the course of the respective treatment. Baseline and post-baseline serum urate levels did not differ in placebo-treated subjects.

Flares of acute gouty arthritis requiring treatment (Figure 1) were most common (approaching 30–40% of subjects) in the four-week study intervals immediately following withdrawal of flare prophylaxis (weeks 9–12 and weeks 13–16) and diminished in frequency thereafter. By the 49- to 52-week study interval, flare rates in subjects with average post-baseline serum urate values less than 6.0 mg/dL were significantly lower than in subjects not achieving this reduction ($p < 0.05$). These findings support a long-term benefit of achieving a serum urate level of less than 6 mg/dL and also support both the efficacy of prophylaxis during early treatment and the recommendation[2,10] for more prolonged prophylaxis in future studies and in clinical practice.

With regard to gout flares, multivariate logistic regression analysis (Table 1) showed that average post-baseline serum urate level, average percent change from baseline serum urate level, and the presence of tophi affected the odds for gout flare, but treatment group assignment and baseline serum urate level did not. The altered risk for flare imparted by the significant variables, however, changed over time of treatment. For example, the presence of tophi increased the odds for flare prior to weeks 25 to 28 but had no significant effect by weeks 49 to 52, perhaps attributable in part to the smaller number of subjects in the combined study population after

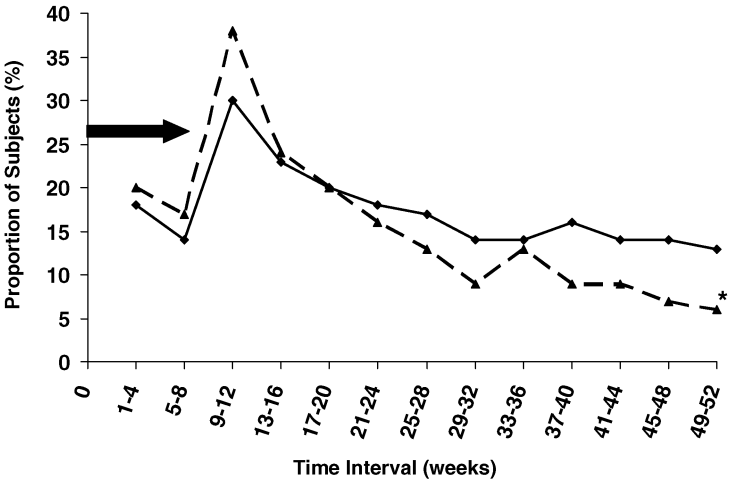

FIGURE 1 Proportions of gouty subjects receiving either febuxostat or allopurinol or placebo in two randomized clinical trials who required treatment for at least one acute flare of gout by four-week trial intervals during the first year of urate-lowering treatment. Gout flare prophylaxis (indicated by arrow) was given for the first eight weeks of the respective study and then discontinued. Triangles on dashed line, subjects with average post-baseline serum urate levels <6.0 mg/dL; squares on solid line, subjects with average post-baseline serum urate levels ≥6.0 mg/dL. *, p <0.05 for the difference between groups at weeks 49 to 52.

completion of the 28-week trial. Average post-baseline serum urate level as well as average percent decrease from baseline serum urate level affected the likelihood for flares throughout the study, in both cases more significantly than the other variables.

With regard to changes in tophus size over time (Table 2), subjects achieving lower post-baseline serum urate levels showed significantly more rapid tophus regression at 28 weeks than subjects who did not. At 52 weeks, however, the effect of lower post-baseline serum urate levels approached but did not reach significance, likely as a result both of fewer subjects remaining for analysis after completion of the 28-week trial and of an increasingly

TABLE 1 Multivariate logistic regression analysis of gout flares requiring treatment in two 4-week trial intervals

	Odds ratio	95% CI	p value
Week 25 to 28			
Avg post-baseline serum urate level	1.42	(1.16, 1.73)	0.0006
Avg % change from baseline serum urate	0.97	(0.95, 0.99)	0.0048
Baseline tophus presence	1.46	(1.03, 2.09)	0.0353
Week 49 to 52*			
Avg post-baseline serum urate level	2.70	(1.72, 4.22)	<0.0001
Avg % change from baseline serum urate	0.92	(0.88, 0.97)	0.0012
Baseline tophus presence	1.59	(0.76, 3.32)	0.2160

*only one of the two studies extended to 52 weeks

TABLE 2 Linear regression analysis of determinants of changes in tophus size

	Parameter	p value
Week 28		
Avg post-baseline serum urate level	4.6274	0.011
Baseline tophus size	−0.0022	0.169
Primary tophus location	—	0.614
Week 52*		
Avg post-baseline serum urate level	6.9636	0.070
Baseline tophus size	−0.0076	0.005
Primary tophus location	—	0.001

*only one of the two studies extended to 52 weeks

significant influence of baseline tophus size and anatomic location on measurement of tophus regression (Table 2).[12]

To clarify the influence of average post-baseline serum urate level on gout flare incidence, an additional analysis of the data set was conducted. Gout flare rates in three specific 4-week trial intervals were recorded according to average post-baseline serum urate levels in the ranges: <4.0 mg/dL; 4.0 to <5.0 mg/dL; 5.0 to <6.0 mg/dL; 6.0 to <7.0 mg/dL; 7.0 to <8.0 mg/dL; and ≥8.0 mg/dL. During weeks 9 to 12, gout flare rates were high (28–42%) among subjects in all ranges of average post-baseline serum urate level. In this study interval, however, a statistically significant trend ($p < 0.001$ by the Cochran-Armitage trend test) toward an inverse relationship between serum urate level and flare incidence was observed. During weeks 49 to 52, however, when flare rates in all serum urate ranges were substantially lower (4 to 18%), the trend had reversed, so that lower flare rates were associated with lower ranges of post-baseline serum urate levels. This trend was also significant ($p = 0.002$). Supporting evidence for a time-related reversal in the risk for flare imparted by post-baseline serum urate level, flare rates at weeks 25 to 28 were not appreciably influenced by average post-baseline serum urate level ($p = 0.158$).

DISCUSSION

Post hoc analyses of data obtained from two large clinical trials comparing urate-lowering agents and placebo have identified significant determinants of clinical outcomes of gout during the first year of treatment. Both absolute and relative post-baseline serum urate levels affect rates of gout flare in treatment year 1, but these influences appear to be distinguishable. Greater relative reductions in serum urate levels impart a persistently increased flare risk. In contrast, the influence of absolute post-baseline serum urate level on gout flare incidence differs with time. Initially, lower serum urate levels are associated with increased risk for flare, but, by the end

of one year, lower serum urate levels decrease the risk for flare. Lower post-baseline serum urate levels were also associated with greater reduction in tophus size at 28 weeks of treatment.

Our findings support a serum urate level <6.0 mg/dL as a target for urate-lowering in gout, but the verification of time-related change in the influence of serum urate levels on gout flare rate is relevant to how this goal is pursued. First, the frequent occurrence of flares underlines the need for the clinician to alert patients initiating urate-lowering treatment to the early increased risk of gout flare. Second, increased flare risk supports the use of means to reduce flare likelihood, such as prophylaxis with colchicine[10] or perhaps a nonsteroidal antiinflammatory agent.[2,8] Third, our findings support the view that the initial goal for urate-lowering treatment may, in many patients, be a modestly subsaturating range of serum urate (such as 4.6–6.0 mg/dL[7]), with upward dose adjustment thereafter as necessary to achieve more rapid tophus dissolution. Whether, as suggested,[13] initiation of low dose urate-lowering agents with titration to goal urate level can substitute for prophylactic medication is a subject warranting future investigation.

The current findings also have relevance to the design of studies of new urate-lowering agents. Because of the increased early flare risk attending urate-lowering therapy in gout, the demonstration of the clinical efficacy of such agents reducing flare incidence will likely require trials of at least a year or more duration.

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