Seminars in Arthritis and Rheumatism 44 (2014) 25–30

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

# Up-titration of allopurinol in patients with gout

Claudine G. Jennings, MBChB[a,*], Isla S. Mackenzie, PhD[a], Rob Flynn, PhD[a], Ian Ford, PhD[b], George Nuki, MD[c], Raffaele De Caterina, MD, PhD[d], Philip L. Riches, MBChB[c], Stuart H. Ralston, MD[c], Thomas M. MacDonald, MD[a], for the FAST study group[1]

[a] Medicines Monitoring Unit (MEMO), University of Dundee, Ninewells Hospital, Dundee DD1 9SY, UK
[b] University of Glasgow, Robertson Centre for Biostatistics, UK
[c] Western General Hospital, Centre for Molecular Medicine, University of Edinburgh, Edinburgh, UK
[d] Cardiovascular Division, G d'Annunzio University, SS. Annunziata Hospital, and Center of Excellence on Aging (Ce.S.I), Chieti, Italy

ARTICLE INFO

*Keywords:*
Gout
Allopurinol
Prescribing
Clinical guidelines

ABSTRACT

*Objectives:* European League against Rheumatism (EULAR) gout management guidelines recommend achieving a target urate level $<6.0$ mg/dL ($<357$ μmol/L). Allopurinol is the most widely used urate-lowering therapy; however, many gout patients who are prescribed allopurinol do not have urate levels optimally controlled. The objective of this analysis was to review the efficacy and tolerability of allopurinol up-titration in achieving the EULAR target levels.

*Method:* The Febuxostat versus Allopurinol Streamlined Trial (FAST) is an ongoing multi-centre study comparing the cardiovascular safety of febuxostat and allopurinol (target recruitment: 5706 patients). Recruited patients were already taking allopurinol and the protocol required up-titration of daily allopurinol dose, in 100 mg increments, to achieve the EULAR urate target level prior to randomisation. We reviewed pre-randomisation data from the first 400 recruited and subsequently randomised FAST patients.

*Results:* Of 400 patients, 144 (36%) had urate levels $\geq 357$ μmol/L at screening and required allopurinol up-titration. Higher urate levels were significantly associated with lower allopurinol dose, male sex, increased BMI, increased alcohol intake and diuretic use. Mean fall in urate levels after a single 100-mg dose increase was 71 μmol/L. The number of up-titrations required ranged from one to five (median = 1) with 65% of patients controlled after one 100-mg up-titration. Overall, 97% of up-titrated patients achieved target urate levels with median final allopurinol dose of 300 mg daily. Side effects and complications of up-titration were minimal.

*Conclusion:* Overall, 36% of FAST patients were not at target urate levels and required up-titration. Allopurinol up-titration was effective in achieving urate target levels and was generally well tolerated by patients.



## Introduction

Gout is a common condition with an overall prevalence in the UK of 1.4% rising to over 6% in the over 65 years age group [1,2]. Incidence of gout in the UK has been stable for the past two decades; however, the disease burden of gout is expected to increase due to increasing life expectancy and a predicted rise in the UK population that is over 60 years of age from 14 million in 2010 to 18.6 million by 2026 [3,4]. The European League against Rheumatism (EULAR) published guidelines in 2006, making a series of recommendations for the management of gout, including titration of urate-lowering therapy to achieve a serum urate target level $<6.0$ mg/dL [5]. The American College of Rheumatology guidelines published in 2012 recommend a target serum urate level $<6.0$ mg/dL in all patients but recognised that lowering serum urate level below 5.0 mg/dL may be required for durable improvements in severe disease manifestations such as tophaceous deposits [6].

Allopurinol is currently the first-line urate-lowering therapy prescribed for patients with chronic gout, and guidelines recommend starting at a low dose and titrating this upwards until a

All listed authors fulfil the requirements for authorship and agree to submission of the manuscript in its current form.

The FAST trial is funded by Menarini and is sponsored by the University of Dundee. IPSEN pharmaceuticals funded the initial protocol development. Both IPSEN and Menarini are permitted an observer at steering committee meetings.

* Corresponding author.
*E-mail address:* claudine@memo.dundee.ac.uk (C.G. Jennings).

[1] Members of the FAST study group are listed at the end of the article.

http://dx.doi.org/10.1016/j.semarthrit.2014.01.004
0049-0172 

target urate level is reached. In the UK, approximately 30% of patients with gout are regularly prescribed allopurinol [7], and it is recognised that a significant proportion of these patients do not achieve the EULAR target of serum urate level $<6.0$ mg/dL. A postal survey in UK primary care practices showed that 23% of patients with gout taking allopurinol had urate levels $>6.0$ mg/dL [8]. In a US review of 15,596 patients with gout, only 30% met the specified urate target level, and of those prescribed allopurinol, 40% did not have the urate level checked after completing their first allopurinol prescription [9]. A survey of UK GPs found that 86% of GPs felt confident in the diagnosis and management of gout [10], but despite this confidence, achievement of the EULAR target levels remains poor. This is potentially due to a lack of awareness of the targets for therapy, concerns about side effects of allopurinol dose increases and infrequent monitoring of urate levels.

The Febuxostat versus Allopurinol Streamlined Trial (FAST) [ISRCTN72443728] fulfils a European Medicines Agency requirement for a post-licensing cardiovascular safety study of febuxostat and compares the cardiovascular safety of febuxostat with allopurinol. Febuxostat is a more potent urate-lowering treatment than 300 mg of allopurinol [11,12]. Therefore, as recruited patients were already taking allopurinol, in order to allow a fair comparison of cardiovascular safety, the study design forced up-titration of allopurinol dose until the serum urate level was below the EULAR target prior to randomisation. An exact conversion of 6.0 mg/dL is 357 μmol/L and this was the cutoff urate level used in FAST.

Analysis of patients recruited into FAST gives an insight into the use of allopurinol in this population and provides important information on the response to allopurinol dose increases, how this therapy is tolerated and what factors might influence patients' response to allopurinol.

## Methods

FAST patients were recruited in Scotland, England and Denmark. Potential patients were identified by searches from primary care databases undertaken by study nurses. Eligible patients were aged over 60 years, prescribed allopurinol for symptomatic hyperuricaemia (clinical diagnosis) and had at least one additional cardiovascular risk factor. Patients with significantly impaired renal function (eGFR $<$ 30 mL/min) were excluded. Patients meeting the inclusion criteria attended for a screening visit, and progression from screening to randomisation was determined by the urate level at screening. If the screening urate level was $<357$ μmol/L (meeting the EULAR urate target level), patients could proceed straight to randomisation; however, if the initial urate level was $\geq 357$ μmol/L, then the daily dose of allopurinol was increased by 100 mg and urate levels were re-checked after 2 weeks on the higher dose. This up-titration process was repeated until the EULAR target urate levels were achieved or the patient reached their maximum-tolerated dose of allopurinol. The maximum possible dose of allopurinol was 900 mg daily, as specified by allopurinol-prescribing guidelines.

Patient data was stored on an electronic clinical report form, and patients were randomised via a central randomisation facility based at the Robertson Centre for Biostatistics, University of Glasgow. Randomisation was 1:1 to take either optimal-dose allopurinol or febuxostat (initially 80 mg with potential to increase to 120 mg to maintain urate levels within the EULAR target range). Patients who required up-titration and all patients for 6 months post-randomisation were offered gout flare prophylaxis with colchicine [second-line prophylaxis was a non-steroidal anti-inflammatory drug (NSAID) with gastric protection]. All patients were encouraged to take 6 months of gout flare prophylaxis; however, it was left to individual patients to decide whether or not to take flare prophylaxis.

The first 400 FAST patients were randomised by January 2013. Data collected from the screening visit and during the up-titration process are presented here. Anonymised data were extracted from the FAST database and analysed using SPSS v. 19. Data describing patient characteristics are shown as mean and standard deviation (SD) or median and inter-quartile range (IQR) as appropriate. Independent *t*-tests and chi-squared (or Mann–Whitney *U* test if appropriate) analysis were used to compare characteristics of patients with urate levels $<357$ μmol/L with those who were not at target levels at screening.

## Results

Of the 400 patients, 144 (36%) had urate levels $\geq 357$ μmol/L at screening and therefore required up-titration of their allopurinol dose. The baseline characteristics of these two groups are shown in the Table.

Patients who required up-titration of allopurinol were significantly more likely to be male ($p = 0.002$), have a higher body mass index (BMI) ($p = 0.026$), have higher alcohol intake ($p < 0.05$), be prescribed a diuretic ($p = 0.015$) and were taking a lower dose of allopurinol ($p < 0.005$) compared with those who were at target levels at the screening visit.

At screening, the maximum prescribed allopurinol dose in this patient population was 600 mg daily. The most commonly prescribed daily doses of allopurinol were 100 mg (in 32% of patients) and 300 mg (in 51% of patients) with only 2% of patients prescribed a daily dose greater than 300 mg (Fig. 1). Overall, 67% of the 129 patients who were prescribed allopurinol 100 mg daily required up-titration compared with 16% of the 203 patients who were prescribed 300 mg. The number of up-titrations required to achieve urate level $<357$ μmol/L ranged from one to five (median $= 1$, mean $= 1.5$). Overall, 65% of up-titrated patients required one dose increase, 24% required two dose increases, 9% required three dose increases and only 1% required more than three dose increases. The maximum final dose of allopurinol required by any patient was 700 mg daily. Figure 2 shows the range of allopurinol doses prescribed at screening and after up-titration for the 144 patients who required up-titration. Overall, 97% of up-titrated patients achieved the EULAR urate target levels. Of the five patients who failed to achieve urate levels $<357$ μmol/L, three did not tolerate further allopurinol dose increases and the other two patients had urate levels of exactly 357 μmol/L at the time of randomisation, and here no further up-titrations were attempted.

The mean fall in urate level after a 100 mg daily dose increase of allopurinol was 71 μmol/L ($\pm 49$ μmol/L). For those patients controlled after a single 100 mg dose increase, the mean fall in urate level was 90 μmol/L ($\pm 43$ μmol/L). Patients requiring only one up-titration had a lower mean baseline urate level of 406 μmol/L compared to 448 μmol/L for those requiring more than one up-titration ($p < 0.05$). The number of up-titrations required was also associated with baseline factors influencing initial urate level, including gender, BMI and diuretic use.

There were no serious adverse events reported for up-titrations of allopurinol, and no patients discontinued allopurinol during the up-titration process. A total of three patients were unable to tolerate further dose increases and reported idiosyncratic side effects, including gastric reflux, paraesthesia and generalised fatigue. Other reported side effects of up-titration included dry skin and mildly deranged liver function tests, but these did not require dose adjustment according to the responsible physician. There were no reported cases of rash or allopurinol hypersensitivity. Overall, three patients (2%) experienced a flare of gout