EXTENDED REPORT

A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout

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Handling editor Tore K Kvien

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2016-210872).

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Received 24 November 2016
Revised 21 February 2017
Accepted 22 February 2017
Published Online First 17 March 2017

ABSTRACT

Objectives To determine the efficacy and safety of allopurinol dose escalation using a treat-to-target serum urate (SU) approach.

Methods A randomised, controlled, parallel-group, comparative clinical trial was undertaken. People with gout receiving at least creatinine clearance (CrCL)-based allopurinol dose for ≥1 month and SU ≥6 mg/dL were recruited. Participants were randomised to continue current dose (control) or allopurinol dose escalation for 12 months. In the dose escalation group, allopurinol was increased monthly until SU was <6 mg/dL. The primary endpoints were reduction in SU and adverse events (AEs).

Results 183 participants (93 control, 90 dose escalation) were recruited. At baseline, mean (SD) urate was 7.15 (1.6) mg/dL and allopurinol dose 269 mg/day. 52% had CrCL<60 mL/min. Mean changes in SU at the final visit were −0.34 mg/dL in the control group and −1.5 mg/dL in the dose escalation group (p<0.001) with a mean difference of 1.2 mg/dL (95% CI 0.67 to 1.5, p<0.001). At month 12, 32% of controls and 69% in the dose escalation had SU <6 mg/dL. There were 43 serious AEs in 25 controls and 35 events in 22 dose escalation participants. Only one was considered probably related to allopurinol. Five control and five dose escalation participants died; none was considered allopurinol related. Mild elevations in LFTs were common in both groups, a few moderate increases in gamma glutamyl transferase (GGT) were noted. There was no difference in renal function changes between randomised groups.

Conclusions Higher than CrCL-based doses of allopurinol can effectively lower SU to treatment target in most people with gout. Allopurinol dose escalation is well tolerated.

Trial registration number:
ANZCTR12611000845932; Results.

INTRODUCTION

Serum urate (SU) lowering is critical in the management of gout with international guidelines recommending SU <6 mg/dL (or <5 mg/dL in the presence of tophi).[1 2] Over time, achieving target SU leads to dissolution of monosodium urate crystals, suppression of gout flares and regression of tophi.

Allopurinol is the most commonly used urate-lowering therapy (ULT). Although allopurinol is US Food and Drug Administration-approved to 800 mg daily, doses > 300 mg daily are used infrequently.[3] Reluctance to increase allopurinol dose is due to physician inertia and concerns about adverse events (AEs), including the rare allopurinol hypersensitivity syndrome (AHS). AHS typically occurs in the first eight weeks after commencing allopurinol and risk factors include higher starting dose and chronic kidney disease (CKD).[4] The relationship between AHS and CKD led to recommendations that the maximum dose of allopurinol should be adjusted according to creatinine clearance (CrCL).[5] These recommendations have been followed widely, but frequently result in failure to achieve target SU.[6]

Uncertainty about the role of CrCL-based allopurinol dosing is reflected in recommendations from the major rheumatology societies. The European League Against Rheumatism 2016 recommendations advocate restricting allopurinol to CrCL-based doses[2] while the American College of Rheumatology recommendations advocate gradual escalation of allopurinol above CrCL-based doses to achieve target SU.[1] The aim of this study was to determine the efficacy and safety of allopurinol dose escalation (DE) in a real-life clinical practice setting.

METHODS

Study design

This paper reports a 12-month, open, randomised, controlled, parallel-group, comparative clinical trial (ANZCTR12611000845932). The study was conducted at two sites in New Zealand with participants enrolled between March 2012 and March 2014. An independent data safety monitoring committee provided oversight.

Participants

People with gout defined by the American Rheumatism Association 1977 preliminary classification criteria for gout[7] receiving at least CrCL-based dose of allopurinol for ≥1 month and with SU ≥6 mg/dL at screening were recruited. People with a history of intolerance to allopurinol and those receiving azathioprine were excluded. CKD was not an exclusion criterion. Participants were recruited from primary and secondary care.

Randomisation and masking

The randomisation sequence was generated electronically by an independent statistician. The

To cite: Stamp LK, Chapman PT, Barclay ML, *et al*. *Ann Rheum Dis* 2017;**76**:1522–1528.

randomisation sequence was stratified by study site and arranged in permuted blocks of size 10. Participants were randomised on a 1:1 ratio to continue the current dose of allopurinol (control) or DE. Randomisation codes were provided to study coordinators in sealed opaque envelopes, which were opened after the participant had consented.

Study treatment and procedures

In the DE group, allopurinol was increased monthly until SU was <6 mg/dL on three consecutive visits or there were AEs. For example, if SU was <6 mg/dL allopurinol was not escalated but if at the following month urate was >6 mg/dL allopurinol was increased unless there was evidence of poor adherence. The dose was increased by 50 mg/d for those with CrCL <60 mL/min and 100 mg/d in those with CrCL ≥60 mL/min. In the control group, participants continued on the same allopurinol dose throughout the study period. Anti-inflammatory prophylaxis and treatment of gout flares were at the discretion of the investigator.

Participants were seen 3-monthly by study coordinators with intervening monthly telephone assessment. At each assessment, concomitant medications, self-reported gout flares and AEs were recorded. Blood was obtained monthly for SU and creatinine and 3-monthly for full blood count and liver function tests. The health assessment questionnaire (HAQ), pain visual analogue scale (pain VAS) and swollen joint count (SJC) and tender joint count (TJC) were completed 3 monthly. Target tophi were identified and the longest axis was measured using Vernier callipers 3 monthly.[8]

Adverse and serious advent event reporting

AEs and serious adverse events (SAEs) were coded according to Common Terminology Criteria for Adverse Events (CTCAE V.4.0). Participants were asked about occurrence of any AEs as well as specific allopurinol-related AEs (abdominal pain, nausea, vomiting, rash and AHS). Laboratory-based allopurinol-related AEs included abnormal liver function, deterioration in creatinine or CrCL and eosinophilia. Treatment-emergent AEs were defined as any AE occurring after entry into the study until the end of month 12. Worsening laboratory AEs were defined as those where there was an increase in CTCAE grade between baseline and month 12. SAEs were defined as an event that was life-threatening, required hospital admission or resulted in death. AEs and SAEs were classified as not related, possibly, probably or definitely related to allopurinol. Management of AEs was at the discretion of the treating physician.

Study outcomes

The primary efficacy outcome was absolute reduction in SU at the final visit (12 months or the final visit for those deceased or lost to follow-up). Secondary efficacy outcomes included (i) the proportion of participants reaching and maintaining target SU levels, defined as the last 3-monthly visits with SU<6 mg/dL, (ii) the percentage reduction in SU at final visit, (iii) the proportion of individuals with any gout flare in the first and last months of randomised treatment and in 3 monthly intervals, (iv) functional status (HAQ), pain VAS, SJC, and TJC changes from baseline to month 12 visit, and (v) index tophus size change from baseline

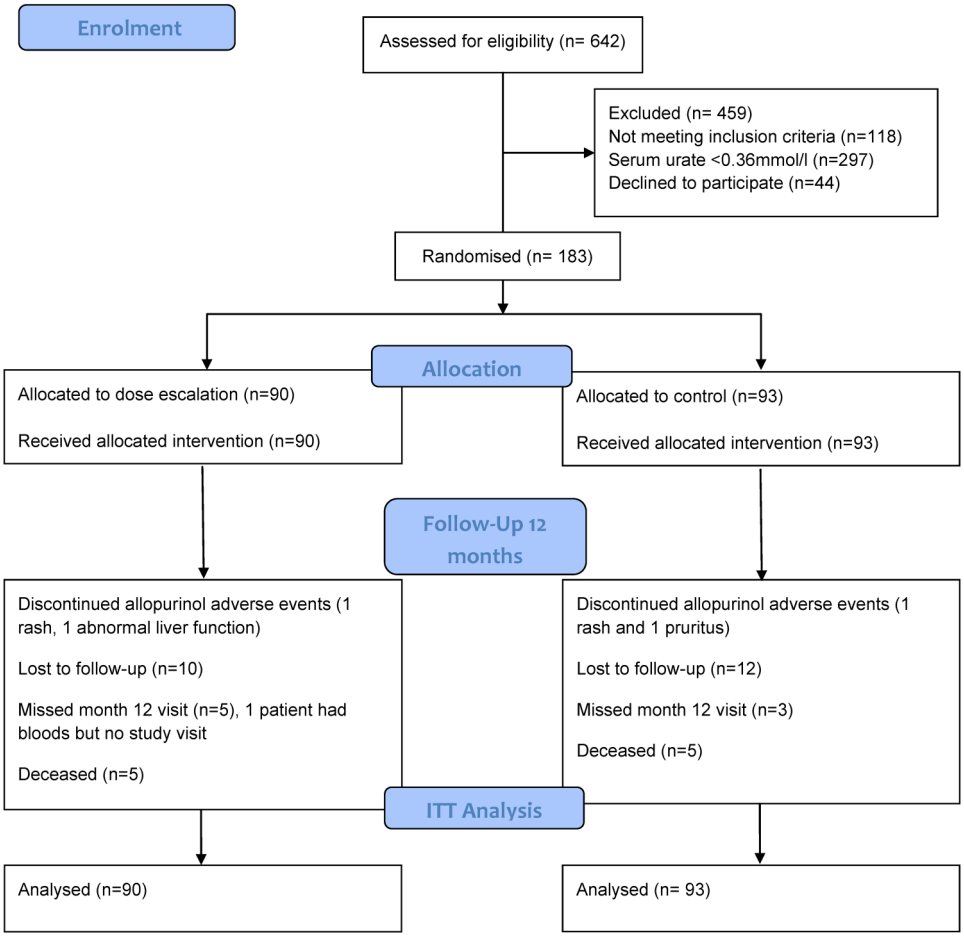

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow of participants. ITT, intention-to-treat.

to 12 months. The SU decremental time-adjusted area under the curve (AUC_{adj-t}) was calculated as a measure of the average improvement in SU for each participant over the study period. The primary safety outcome was treatment emergent or worsening AEs, serious and non-serious.

Sample size and power

A planned sample size of 200 participants (~100/group) was calculated to enable a difference in the decline in SU over 12 months greater than 0.67 mg/dL to be detected as statistically significant (2 tailed $\alpha=0.05$) with 80% power based on data from the previous pilot study.[9] This allowed for up to 10% attrition over the period of the study. Further, we estimated that a difference of 35% or more in the percentage achieving the target SU between the DE and control groups would be detected as statistically significant (2 tailed $\alpha=0.05$) with power >90%.

Statistical analysis

Baseline demographics and clinical features were summarised using standard descriptive statistics including means, SD, median, range, number and percent as appropriate. All randomised participants were included within the intention-to-treat analysis population and analysed within their randomised group. The primary efficacy outcome, absolute reduction in SU, was compared between randomised groups using a general linear model which included randomised group and study site as fixed factors and baseline SU as a covariate. The proportions of participants achieving and maintaining target SU levels, the proportion experiencing a gout flare and the proportion with a tophus were compared between randomised groups using logistic regression models with site as the stratification variable. The change in HAQ, pain VAS, SJC, TJC, and index tophus size from baseline to month 12 and SU decremental AUC_{adj-t} were compared between randomised groups using a general linear model which included site and randomised group as fixed factors and baseline SU as a covariate. The statistical analysis plan is available as online supplementary material.

RESULTS

Participant characteristics

Of the 642 participants screened, 183 were randomly assigned to control (n=93) or DE (n=90) (figure 1). All randomised participants received at least one dose of allopurinol. Two participants in the control group and two in the DE group discontinued allopurinol (figure 1). In the control group, protocol violations were recorded for seven participants who had the dose of allopurinol increased (by healthcare practitioners outside the study setting). Five participants in the DE group were not dose escalated as SU post-screening was <6 mg/dL. For the remainder of the participants allopurinol was increased as per the protocol.

The baseline demographic and clinical features were well matched between randomised groups (table 1). Mean (SD) SU was 7.2 mg/dL (1.6), in 51.9% of participants CrCL was <60 mL/min and in 13.1% CrCL was <30 mL/min. A number of participants had baseline laboratory abnormalities; the majority of these were mild with exception of creatinine (see online supplementary table S1).

Efficacy

Primary endpoint

The mean change in SU at the final visit was −0.34 mg/dL in the control group and −1.5 mg/dL in the DE group (p<0.001) with a mean difference of 1.2 mg/dL (95% CI 0.67 to 1.5), p<0.001). In the control group mean (SD) SU was 7.13 (1.6) mg/dL at baseline and 6.9 (1.5) mg/dL at final visit, compared with 7.18 (1.6) mg/dL and 5.7 (1.2) mg/dL in the DE group (figure 2A).

Secondary endpoints

SU was <6 mg/dL at the final visit in 32% of the control group and 69% in the DE group (p<0.001); OR 4.3 (95% CI 2.4 to 7.9). The mean allopurinol dose of those at target was 390 (50–

Table 1 Participant baseline demographics and clinical features

Variable	Control (n=93)	Dose escalation (n=90)	All participants (n=183)
Age years*	60.9 (12.8)	59.5 (12.1)	60.2 (12.5)
Male, n (%)	78 (84%)	82 (91%)	160 (87.4%)
Ethnicity, n (%)			
NZ European	39 (42%)	37 (41%)	76 (41.5%)
Maori	22 (24%)	29 (32%)	51 (27.9%)
Pacific Island	27 (29%)	19 (21%)	46 (25.1%)
Asian	4 (4%)	5 (6%)	9 (4.9%)
Other	1 (1%)	0 (0%)	1 (1.1%)
Duration of gout (years)	17.9 (13.2)	16.5 (11.3)	17.2 (12.3)
Baseline serum urate mg/dL*	7.13 (1.6)	7.18 (1.6)	7.15 (1.6)
Creatinine (mg/dL)*	1.47 (1.02)	1.58 (0.11)	1.58 (1.02)
CrCL (mL/min)	60.3 (27.7)	60.1 (27.3)	60.2 (27.4)
Body mass index (kg/m^2)*	35.2 (7.4)	35.2 (7.9)	35.2 (7.7)
Flare frequency in the preceding year (median, IQR)	4 (1.3–11.8)	3 (1.0–5.3)	3 (1–8)
Baseline allopurinol dose mg/day†	275.8 (100–600)	261.9 (100–600)	269.0 (100–600)
Allopurinol dose mg/day n (%)			
100–200	31 (33.3%)	37 (41.1%)	68 (37.2%)
>200–300	50 (53.4%)	47 (52.2%)	97 (53%)
>300	12 (12.9%)	7 (7.7%)	19 (10.4%)
Presence of palpable tophi n (%)	46 (49%)	35 (39%)	81 (44.2%)
Coexisting conditions n (%)			
Obesity‡	70 (75%)	64 (71%)	134 (73.2%)
CrCL <60 mL/min	45 (48%)	50 (56%)	95 (51.9%)
CrCL <30 mL/min	14 (15%)	10 (11%)	24 (13.1%)
Kidney stones	3 (10%)	5 (14%)	8 (12.3%)
Cardiovascular disease§	38 (41%)	41 (46%)	79 (43.2%)
Diabetes	33 (36%)	29 (32%)	62 (33.9%)
Hypertension	65 (70%)	67 (74%)	132 (72.1%)
Hyperlipidaemia	58 (62%)	47 (52%)	105 (57.4%)
Concurrent medications n (%)			
Diuretic	43 (46%)	38 (42%)	81 (44.3%)
Aspirin	41 (44%)	40 (44%)	81 (44.3%)
Any anti-inflammatory prophylaxis	45 (48%)	51 (57%)	96 (52.5%)
Colchicine	35 (38%)	34 (38%)	69 (37.7%)
Non-steroidal anti-inflammatory drugs	9 (10%)	15 (17%)	24 (13.1%)
Prednisone	12 (13%)	12 (13%)	24 (13.1%)

*Mean (SD).
†Mean (range).
‡Obesity defined as body mass index ≥30 kg/m^2.
§Cardiovascular disease defined as ischaemic heart disease, heart failure or peripheral vascular disease.
CrCL, creatinine clearance.

900) mg daily compared with 290 (0–700) mg daily in those not at target (p<0.001).Time course of achieving target SU is shown in figure 2B. SU <6 mg/dL at each of the last 3 monthly visits was achieved by 14% of the control group and 59% of the DE group (p<0.001); OR 8.0 (95% CI 3.6 to 17.7). The mean percentage change in SU from baseline to final visit was −3.3% in the control group compared with −17.8% in the DE group (p<0.001) with a mean difference of 14.5% (95% CI 8.4 to 20.6%) (figure 2C). There was a significantly higher $AUC_{adj\text{-}t}$ in the DE group compared with the control group (0.99 vs 0.29 mg/dL; p<0.001) with a mean difference of 0.69 mg/dL (95% CI 0.42 to 0.96). The mean final dose of allopurinol was 288 mg/day (0–600 mg/day) in the control group and 413 mg/day (0–900 mg/day) in the DE group (figure 2D).

Gout flares and other activity measures

During the study period, 59% of the control group and 54% of the DE group experienced at ≥one self-reported gout flare (p=0.58) (see online supplementary figure S1A). By the end of the study period there had been a reduction in use of prophylaxis in both groups (see online supplementary figure S1B). There was no significant difference in the mean change in index tophus size over the study period between randomised groups (see online supplementary figure S1C). Of those with measurable tophi, complete resolution of tophi occurred in 8/43 (19%) of the control group and 6/32 (19%) of the DE group. There was no significant difference in the mean change from baseline to 12 months between randomised groups for HAQ, pain VAS, SJC or TJC (see online supplementary table S2).

Safety

Serious adverse events

There were 43 SAEs in 25 control participants and 35 in 22 DE participants (tables 2 and 3). Five participants in each group died. None of the deaths was attributed to allopurinol. In the control group, deaths were attributed to sepsis (n=2), heart failure (n=1), respiratory failure (n=1) and long-standing CKD refusing dialysis (n=1). In the DE group, deaths were attributed to heart failure (n=2), myocardial infarction (n=2) and aortic dissection (n=1). One SAE was considered probably related to allopurinol, increase in international normalised ratio (INR) in a DE participant who commenced warfarin after elective mitral valve replacement.

Non-laboratory AEs

There were 336 non-laboratory AEs in 80 control participants and 339 in 73 DE participants (table 2 and online supplementary table S3). The number of participants experiencing at least one non-laboratory AE in each CTCAE category is shown in table 2. In the control group, 11 participants developed rash; one was considered probably related to allopurinol and allopurinol was discontinued. Five participants in the control group developed pruritus, one was considered probably related to allopurinol. In the DE group, eight participants developed rash, two were considered possibly related but resolved despite continuing allopurinol and one was probably related and allopurinol was discontinued. Ten participants in the DE group developed pruritus, of which one was considered possibly related to allopurinol.

Of the other non-laboratory AEs, one was definitely related; a DE participant who accidentally took 2–3 times the prescribed dose of allopurinol for 2 days after confusing medication bottles. There were no clinical sequelae. Two DE participants had malaise possibly related to allopurinol; one of these participants also had a headache possibly related to allopurinol. One DE participant had vertigo, nausea and abdominal pain probably related to allopurinol. No other non-laboratory AEs were thought to be related to allopurinol.

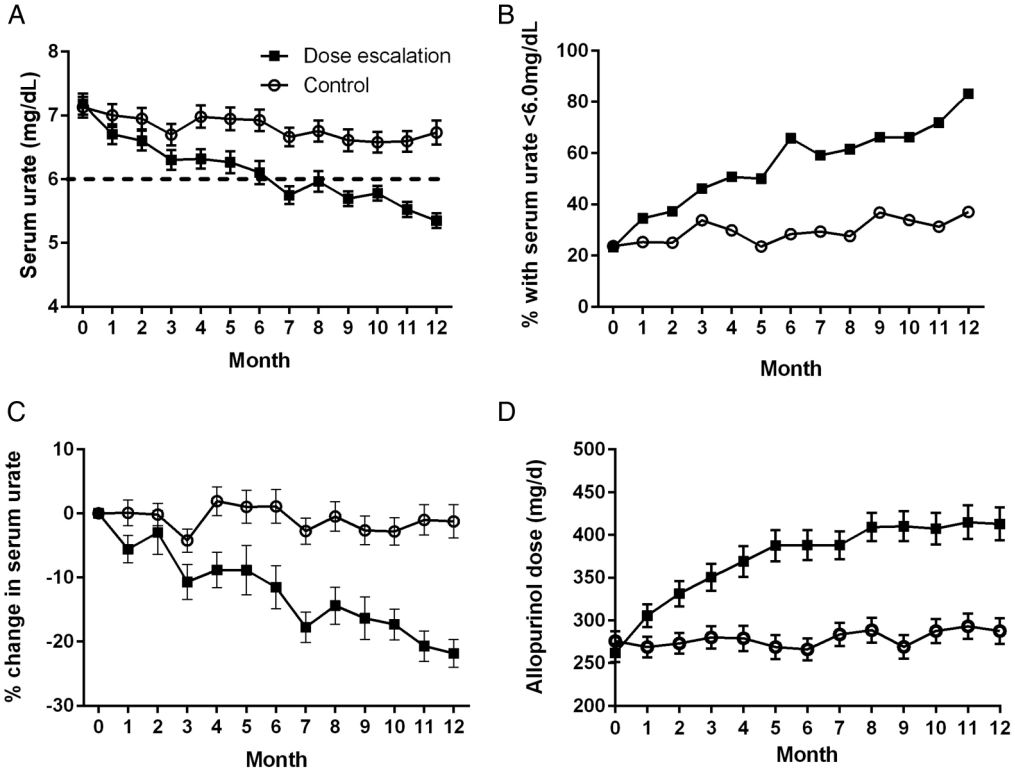

Figure 2 Mean serum urate (A), time course for achieving target serum urate (B), mean percentage change in serum urate (C) over the 12-month study period and (D) mean allopurinol dose in control and dose escalation groups.

Laboratory AEs

For the 3-monthly visits, there were 56 liver function treatment-emergent or worsening AEs in 28 control participants and 77 in 32 DE participants. For aspartate aminotransferase (AST), alanine transferase (ALT) and alkaline phosphatase (ALP), the majority were CTCAE grade 1 (figure 3A–D). For gamma glutamyl transferase (GGT), there were 19 abnormalities in 12 control participants and 36 in 19 DE participants, of which 3 participants in the DE group increased by two CTCAE grades.

For creatinine, an increase from baseline value was used to determine CTCAE grade. From the monthly visits, there were 465 events in 82 control participants and 452 events in 81 DE participants; >96% were grade 1 (>1–1.5× above baseline) (figure 3E). There were 28 control participants and 34 DE participants who experienced more than a 20% decrease in CrCL at any stage over the study (figure 3F). A similar proportion of participants had an increase in CrCL (figure 3F).

Haematological treatment-emergent or worsening AEs included eosinophilia, anaemia, thrombocytopenia, neutropenia and lymphopenia. From the 3-monthly visits, there were 45 events in 25 control participants and 65 events in 30 DE participants (see online supplementary table S4 and figure S2). Eosinophilia occurred in 15 control participants and 14 DE participants at some stage during the 12-month period (figure 3G).

Improvement in laboratory variables

A number of laboratory variables improved during the study. A 20% improvement in CrCL at some point during the 12 months was observed in 24 control participants and 18 DE participants (figure 3F). Of those with abnormal GGT at baseline, 16/33 participants in the control group and 13/39 participants in the DE group improved by at least one CTCAE grade during the study.

DISCUSSION

We have shown that DE of allopurinol is effective in people with gout, including in those with CKD, with 69% achieving target SU at final visit and 59% achieving and maintaining SU <6 mg/dL at the last 3-monthly visits. A number of DE participants failed to achieve target SU; this may reflect poor adherence or true resistance to allopurinol. A small number of control participants achieved target urate, most likely reflecting improved compliance or simply variation in SU around the target.

Table 2 Number (%) of participants with at least one serious adverse event and the number (%) of individuals in each category and non-laboratory adverse events summary; number of participants (%) with at least one event during the study period

	Serious adverse event		Non-laboratory treatment emergent adverse event	
	Control (n=93)	Dose escalation (n=90)	Control (n=93)	Dose escalation (n=90)
Number of participants with at least one adverse event	25 (27%)	22 (24%)	80 (86%)	73 (81%)
Cardiac disorders	8 (9%)	11 (12%)	9 (10%)	5 (6%)
Gastrointestinal disorders	6 (7%)	3 (3%)	21 (23%)	18 (20%)
General disorders	1 (1%)	1 (1%)	47 (51%)	48 (53%)
Hepatobiliary disorders	0	1 (1%)	0	2 (2%)
Infections and infestations	8 (9%)	3 (3%)	18 (19%)	14 (16%)
Injury, poisoning and procedural complications	2 (2%)	1 (1%)	15 (16%)	24 (27%)
Investigations	0	1 (1%)		
Metabolism and nutrition	0	2 (2%)	4 (4%)	1 (1%)
Musculoskeletal	1 (1%)	1 (1%)	27 (29%)	24 (27%)
Nervous system disorders	3 (3%)	1 (1%)	10 (11%)	11 (12%)
Renal and urinary disorders	5 (5%)	2 (2%)	0	2 (2%)
Respiratory, thoracic and mediastinal disorders	2 (2%)	2 (2%)	16 (17%)	15 (17%)
Skin and subcutaneous tissue disorders	1 (1%)	1 (1%)	20 (22%)	23 (26%)
Blood and lymphatic system			0	1 (1%)
Ear and labyrinth			3 (3%)	3 (3%)
Endocrine			0	1 (1%)
Eye			4 (4%)	3 (3%)
Immune system			1 (1%)	1 (1%)
Neoplasms benign, malignant and unspecified			4 (4%)	4 (4%)
Psychiatric disorders			5 (5%)	4 (4%)
Reproductive and breast disorders			2 (2%)	0
Surgical and medical procedures			2 (2%)	2 (2%)
Vascular disorders			8 (9%)	10 (11%)
Venous disorders			1 (1%)	0
Allopurinol-specific adverse events				
Allopurinol hypersensitivity syndrome			0	0
Rash			11 (12%)	8 (9%)
Pruritus			5 (5%)	10 (11%)
Nausea/vomiting			9 (10%)	6 (7%)
Abdominal pain			5 (5%)	6 (7%)

Table 3 Number of serious adverse events in each Common Terminology Criteria for Adverse Events category

	Control (n=93)	Dose escalation (n=90)
Cardiac disorders	14	14
Gastrointestinal disorders	6	3
General disorders	1	1
Hepatobiliary disorders	0	1
Infections and infestations	8	4
Injury, poisoning and procedural complications	2	1
Investigations	0	1
Metabolism and nutrition	0	2
Musculoskeletal	1	1
Nervous system disorders	3	1
Renal and urinary disorders	5	2
Respiratory, thoracic and mediastinal disorders	2	2
Skin and subcutaneous tissue disorders	1	2

As with all ULT clinical trials,[10–13] the primary efficacy endpoint in this study was SU lowering. Although the majority of the DE group achieved target SU, there was no significant reduction in gout flares during the study period. Importantly, there was no difference between the DE and control groups with regard to flares. Previous studies have shown an increase in flare rate after staring ULT[10 11] and that flares can persist for several years after SU target is achieved.[14] Likewise, there was no difference in tophus regression, HAQ and joint counts between groups. These results are similar to other clinical trials of oral ULT,[10 13 14] which show it takes longer than 12 months for changes in these outcomes to occur. As about half the participants had CrCL <60 mL/min, the escalation of allopurinol was slow (50 mg per month) so mean SU <6 mg/dL was not reached until month 7 which may have affected outcomes. A longer observation period is likely to be necessary to see any difference in flare rates. An open-label extension phase of this study will further address these endpoints.

There were a number of SAEs in both groups, although only one was related to allopurinol. No new safety signal was identified. There were no cases of AHS; however, the study was not powered to detect AHS, which is rare (<0.1%) and usually occurs within 8 weeks after starting allopurinol.[4] Participants in this study had been on allopurinol for ≥1 month prior to enrolment. Given the rarity of AHS, it is unlikely that any allopurinol DE study will be undertaken that is sufficiently powered to detect this specific SAE. There were a number of participants in both groups who developed rashes and pruritus. However, only two participants discontinued allopurinol, highlighting how common and non-specific rash and itch are. It is important to note that management of these AEs was at the discretion of the treating physician; in most cases, allopurinol was reduced with subsequent rechallenge to be sure symptoms were not allopurinol related.

A number of treatment-emergent liver function abnormalities occurred. For AST, ALT and ALP, the majority of these were mild and similar between randomised groups. There were more elevations in GGT and a small number of higher-grade abnormalities in the DE group compared with controls. An increase in GGT was also noted in the LASSO study.[15] The clinical significance of these elevated GGTs remains unclear particularly in this group of patients with multiple comorbidities which might contribute to increases. GGT is an inducible enzyme, and allopurinol at higher doses may contribute to this induction.

There were a large number of creatinine AEs during the study using the definition of change from baseline. This definition results in some individuals with creatinine levels well within the laboratory normal reference range having an 'adverse event'. Approximately 10% of individuals had a decrease in CrCL

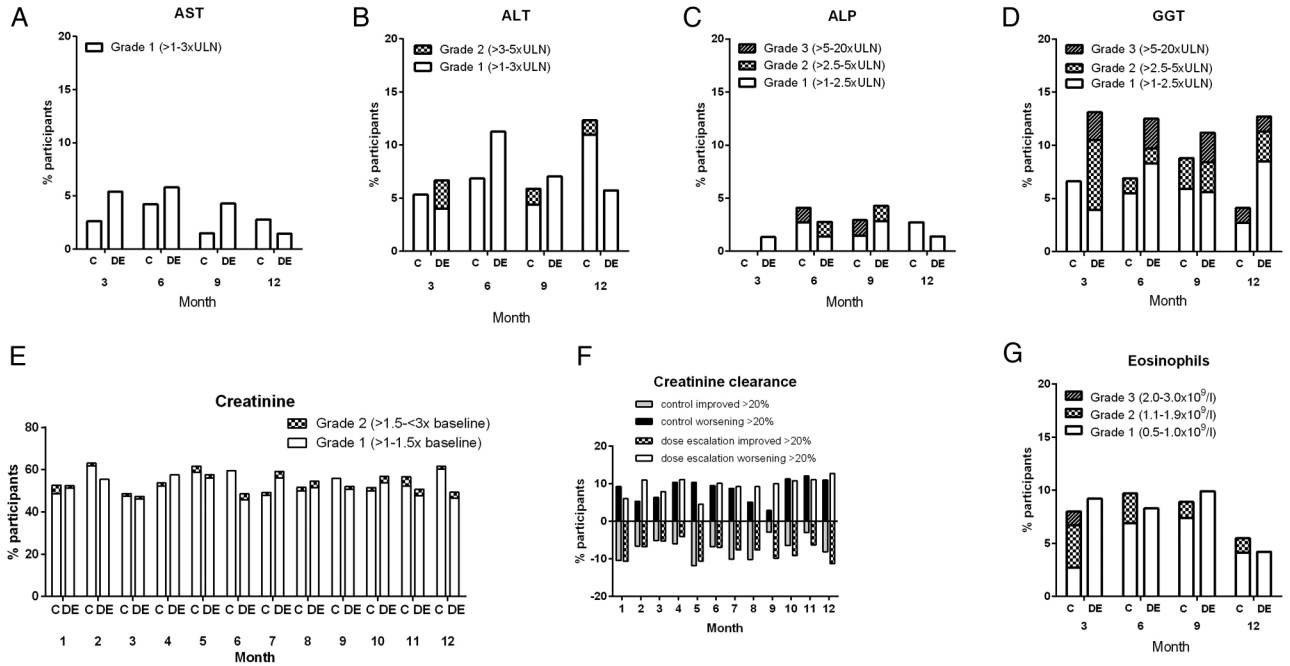

Figure 3 Treatment-emergent or worsening laboratory adverse events: (A–D) liver function over the 12-month study period by Common Terminology Criteria for Adverse Events grade in control and dose escalation (DE) groups. (E) Percentage of participants with increase in creatinine over baseline and (F) percentage of participants with more than a 20% decrease (worsening) or increase (improvement) in creatinine clearance from baseline and (G) percentage of participants with eosinophilia. C, control.

≥20% with no obvious difference between groups. Importantly, similar numbers of individuals had an improvement in CrCL.

There are a number of limitations of this study. The study was not blinded and thus carries the inherent risks of bias in an open-label study. However, the primary endpoint was a laboratory value which is not open to bias. The main source of bias was around attribution of AEs to allopurinol. It is possible that AEs were more likely to be attributed to allopurinol in the DE group than the control group.

One of the key strengths of this study is the population which has a high prevalence of comorbid conditions, particularly CKD (52% having CrCL<60 mL/min and at least some of these having CKD stage 3 or higher) as well as severe gout (44% with tophi). Data from NHANES 2007–2008 showed that of the individuals with gout 74% had hypertension, 71% had ≥stage 2 CKD, 53% were obese, 26% had diabetes, 14% had a history of myocardial infarction and 10% had a history of stroke.[16] Thus our population is representative of people with gout, represents real-life clinical practice and the results are generalisable to other gout populations.

In conclusion, in people with gout, including those with kidney impairment, who tolerate CrCL-based doses of allopurinol but fail to reach target urate, gradual DE to achieve target urate is effective and well-tolerated.

Acknowledgements The authors are grateful to the Health Research Council of New Zealand Independent Data Safety Monitoring Committee for monitoring the study.

Contributors LKS and ND: literature search, study design, data collection, data analysis, data interpretation and manuscript preparation. PTC and JD: study design, data collection, data analysis, data interpretation and manuscript preparation. MLB and CF: study design, data analysis, data interpretation and manuscript preparation. AH and PT: data collection, data analysis, data interpretation and manuscript preparation.

Funding This study was funded by the Health Research Council of New Zealand (11/203).

Competing interests LKS reports grants from Health Research Council of New Zealand, during the conduct of the study; grants from Ardea Biosciences, grants from Health Research Council of New Zealand, outside the submitted work; AH reports grants from Health Research Council of New Zealand, during the conduct of the study; ND reports grants from Health Research Council of New Zealand, during the conduct of the study; grants from Health Research Council of New Zealand, grants and personal fees from AstraZeneca, grants and personal fees from Ardea Biosciences, personal fees from Takeda, personal fees from Teijin, personal fees from Menarini, grants from Fonterra, personal fees from Pfizer, personal fees from Crealta, personal fees from Cymabay, outside the submitted work.

Patient consent Obtained.

Ethics approval MultiRegional Ethics Committee of New Zealand.

Provenance and peer review Not commissioned; externally peer reviewed.

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A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout

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*Ann Rheum Dis*2017 76: 1522-1528 originally published online March 17, 2017
doi: 10.1136/annrheumdis-2016-210872

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