

A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout

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ABSTRACT

Objectives: To compare the efficacy and tolerability of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day used to attain a target serum urate concentration (sUr) ≤ 0.30 mmol/l (5 mg/dl).

Methods: A randomised, controlled, open-label, multicentre trial in gout patients with renal function defined as a calculated creatinine clearance ≥ 50 ml/min. Patients were treated with 300 mg allopurinol or 100 mg benzbromarone once a day (stage 1). If sUr ≤ 0.30 mmol/l was not attained after 2 months, the dose was doubled to allopurinol 300 mg twice a day or benzbromarone 200 mg once a day (stage 2). The primary end point was treatment success in either of the two stages, defined as clinical tolerability and attainment of biochemical target sUr.

Results: Sixty-five patients were enrolled in stage 1; 36 received allopurinol and 29 received benzbromarone. Fifty-five patients (85%) were analysed at stage 1: the success rates were 8/31 (26%) and 13/25 (52%), respectively, and the difference was -0.26 (95% CI from -0.486 to -0.005), $p = 0.049$. At stage 2, the success rates were 21/27 (78%) and 18/23 (78%), respectively, and the difference was -0.005 (95% CI from -0.223 to 0.220), $p = 1.00$. Two patients stopped receiving allopurinol and three stopped receiving benzbromarone because of adverse drug reactions.

Conclusions: Increasing the allopurinol dose from 300 to 600 mg/day and the benzbromarone dose from 100 to 200 mg/day according to the target sUr produced significantly higher success rates (both 78% successful in attaining sUr ≤ 0.30 mmol/l). No significant differences in treatment success between benzbromarone and allopurinol were found after dose escalation.

Trial registration number: ISRCTN49563848).

Allopurinol is the drug of choice in the long-term treatment of gout in the 2006 EULAR evidence-based recommendations.¹ Quite similar recommendations are given by the British Society of Rheumatology, with a remarkably lower biochemical target for serum urate concentration (sUr; 0.30 vs 0.36 mmol/l).² In order to reach the target sUr, the EULAR recommendations advise titrating the allopurinol dose up to a maximum of 900 mg/day. However, historically a fixed dose of 300 mg/day is mostly used in clinical research and clinical practice.³ Data on clinical efficacy and tolerability of urate-lowering treatment are scarce, especially for higher than standard doses.⁴ In one study, allopurinol 600 mg/day was given to 19 patients,

resulting in a mean (SD) sUr decrease of 44 (13)% compared with baseline and 52% success in attaining sUr ≤ 0.30 mmol/l.⁵ In a dose-response study in patients with heart failure, sUr decreased from 0.41 (0.11) mmol/l to 0.16 (0.06) mmol/l when allopurinol 600 mg/day was used.⁶ In a randomised controlled trial of benzbromarone 200 mg/day versus probenecid 2000 mg/day (ISRCTN21473387, www.controlled-trials.com), we found a decrease in sUr of 64 (9)% compared with baseline, and 92% success in attaining sUr ≤ 0.30 mmol/l.⁷

The goal of sUr-lowering treatment is to reduce the sUr to below the threshold of supersaturation to prevent any gouty attack by allowing the dissolution of existing monosodium urate crystals in the joints and to stop the deposition of new crystals.^{8–15} The solubility of urate in joint fluids is influenced by temperature, pH, concentration of cations, level of articular dehydration and the presence of nucleating agents such as insoluble collagens, chondroitin sulphate and non-aggregated proteoglycans.⁸ The occurrence of acute gout attacks depends on the sUr attained and mechanical stress, as joints affected by osteoarthritis may be predisposed to attacks.^{9–10}

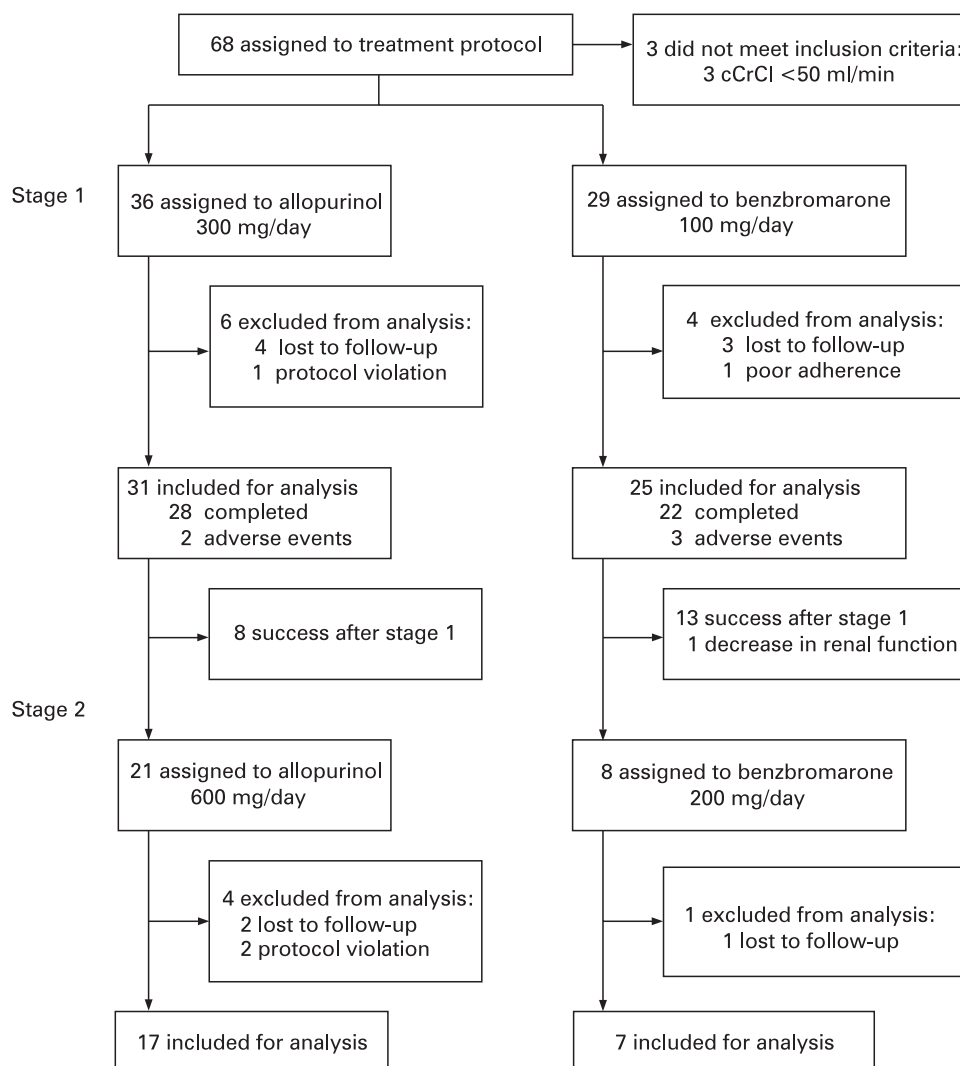
According to the EULAR 2006 recommendations, the goal of sUr-lowering treatment is to reach a target sUr of <0.36 mmol/l (6.1 mg/dl).¹ Historically, the target sUr is based on the solubility of monosodium urate. For instance, the threshold level of deposition of monosodium urate is 0.36 mmol/l at 35°C and 0.27 mmol/l at 30°C.¹⁴ However, gout attacks mostly occur in the extremities, where body temperature is lowest and the solubility of monosodium urate is lowest. It has been shown that recurrent gouty attacks are more effectively prevented and that tophi dissolve more quickly with a target sUr of <0.30 mmol/l (5.0 mg/dl) compared with levels of 0.30–0.36 mmol/l.^{15–19} For this reason, the British Guideline 2007 sets the sUr treatment goal for patients with gout at ≤ 0.30 mmol/l.²

In order to obtain more evidence-based data, we investigated the efficacy and tolerability of dose escalation of allopurinol versus benzbromarone to attain a target sUr of ≤ 0.30 mmol/l.

PATIENTS AND METHODS

This prospective, multicentre, open-label, randomised controlled trial was carried out in successive

Figure 1 Flow of participants through each stage of the study. cCrCl, calculated creatinine clearance.



previously untreated patients with gout recently diagnosed by a rheumatologist. Eligibility criteria were: (1) a diagnosis of gout, confirmed by microscopic evidence of urate crystals in punctate from synovial fluid or peri-articular structures or the presence of tophi; (2) no history of having used one of the study drugs; (3) no relevant liver disease; (4) renal function defined as a calculated creatinine clearance (cCrCl) ≥ 50 ml/min calculated using the formula of Cockcroft and Gault; (5) an indication for sUr-lowering treatment—presence of tophi or frequent attacks (>2 /year).^{20–23} Before the patients entered the study and after each treatment period, liver function, serum creatinine and cCrCl, sUr, urinary creatinine excretion and urinary urate excretion on an unrestricted purine diet were measured. In patients using allopurinol, serum oxipurinol concentrations were also measured after each treatment period. Underexcretion of urate was defined as urate clearance <6.0 ml/min per 1.73 m².²⁴ This was calculated from the urinary volume (converted into ml/min) \times (urinary urate concentration/sUr) and normalised for a body surface area of 1.73 m². Overproduction of urate was defined as urinary urate excretion >6.0 mmol/day. Normal excretion of urate was defined as urate clearance ≥ 6.0 ml/min per 1.73 m² and urinary urate excretion ≤ 6.0 mmol/day. Reported adverse events were checked for causality by the Naranjo Causality Scale.²⁵ Those classified as doubtful were not included as adverse drug reactions in the tolerability evaluation.

At the time of inclusion in the study, patients were assigned an inclusion number by the rheumatologist (blinded) and subsequently randomised to allopurinol or benzbromarone treatment. A computer-generated central randomisation schedule with a block size of six was used. Study recruitment and follow-up were from July 2006 until December 2007.

Patients were given allopurinol 300 mg (several generic brands) in a step-up dose scheme (100 to 200 to 300 mg/day, dose raised every week) or benzbromarone 100 mg once a day (Desuric; Prostrakan, Galashiels, UK). If treatment was tolerated but the treatment goal of sUr ≤ 0.30 mmol/l was not reached after 2 months, the allopurinol dose was doubled to 300 mg twice a day and the benzbromarone dose to 200 mg once a day. The dose interval of allopurinol was set at twice a day at the higher dose because this is recommended in the product information. Also, from a pharmacodynamic point of view, administration twice a day yields higher serum trough concentrations, which may result in greater enzyme inhibition. Treatment was evaluated again after 2 months. If treatment was not tolerated and the patient stopped the treatment, this was categorised as a failure. If treatment was tolerated and the target sUr was reached, this was categorised as a success. Defined daily doses are allopurinol 400 mg/day and benzbromarone 100 mg/day.

Prophylaxis of gouty episodes with colchicine 0.5–1 mg/day was prescribed until the target sUr was reached (≤ 0.30 mmol/l);

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Table 1 Details and clinical characteristics of the study participants

	Allopurinol (n = 36)	Benzbromarone (n = 29)
Age (years)	58.6 (12.3)	59.6 (11.3)
Male (%)	81	83
Tophaceous gout (%)	53	48
Recurrent flares (%)		
0–2/year	18	17
3–5/year	59	50
>5/year	22	33
Body mass index (kg/m ²)	29.4 (4.8)	30.5 (6.9)
cCrCl (%)		
30–50 ml/min	(3 excluded)	(0 excluded)
50–80 ml/min	22	39
>80 ml/min	78	61
Research site (%)		
Medisch Centrum Leeuwarden	28	24
Ziekenhuisgroep Twente	41	45
Medisch Spectrum Twente	31	31
Urate characteristics		
sUr (mmol/l)	0.54 (0.09)	0.51 (0.08)
Range	0.39–0.83	0.34–0.70
uUr (mmol/day)	3.4 (1.3)	3.4 (1.3)
Range	1.5–7.7	1.3–6.3
UrCl (ml/min/1.73 m ²)	3.7 (1.3)	3.9 (1.3)
Range	1.5–6.8	1.6–6.4
Excretor type (%)		
Underexcretor	94	89
Normal excretor	3	3
Overproducer	3	8

Data are mean (SD) or percentage, unless stated otherwise.

cCrCl, calculated creatinine clearance; sUr, serum urate; UrCl, urate clearance; uUr, urate excreted in urine.

if colchicine was not tolerated, a non-steroidal anti-inflammatory drug could be prescribed as an alternative.

The primary end point was the percentage of patients who tolerated the sUr-lowering medication and attained sUr ≤ 0.30 mmol/l after stage 1 or stage 2. The secondary end point was the relative decrease in sUr attained with each treatment regimen.

Statistical analysis

A power calculation indicated that at least 22 patients were needed for evaluation in each treatment arm to prove a statistically significant difference between allopurinol and benzbromarone (based on an estimated 55% success rate for allopurinol 600 mg/day versus 90% for benzbromarone 200 mg/day, $\alpha = 0.05$, $\beta = 0.20$).^{5–7} We expected a loss to follow-up of 25%, rendering a minimum of 60 patients required for the study. SPSS V15.0 and V16.0 for Windows were used for data collection, data validation, data selection and statistical analysis. The Student two-sided t test and Fisher–Boschloo unconditional test were used to compare the effectiveness of allopurinol and benzbromarone; 95% CIs of proportions were calculated using binomial distribution, and 95% CIs of differences of proportions using the Agresti–Caffo method.^{26–27} Normality was verified by Kolmogorov–Smirnov analysis. $p < 0.05$ was considered significant.

The study was approved by the medical ethical review board of the participating hospitals, and written informed consent was obtained from all participating patients.

RESULTS

Sixty-eight patients were enrolled in the study (fig 1). Three did not meet the inclusion criteria (cCrCl was < 50 ml/min), leaving sixty-five patients for analysis of baseline characteristics (table 1). Thirty-six patients received allopurinol and 29 received benzbromarone. Fifty-five patients (85%) were eligible for analysis of stage 1 results and 50 patients (77%) for analysis of stage 1+2.

Table 2 and fig 2 give the results of stage 1 and 2. The treatment target was reached in eight out of 30 patients (26%) using allopurinol 300 mg/day; after the increase in dose to 600 mg/day, the overall treatment success was 21 out of 27 patients (78%). With benzbromarone 100 mg/day, the treatment target was reached in 13 out of 25 patients (52%); after the increase in dose to 200 mg/day, the overall treatment target was reached in 18 out of 23 patients (78%). Two patients stopped receiving allopurinol and three stopped receiving benzbromarone because of adverse drug reactions (table 3). No additional adverse drug reactions were reported after the increase in doses of allopurinol and benzbromarone. At stage 1, the success rates were $8/31 = 0.26$ and $13/25 = 0.52$; the difference was $0.26 - 0.52 = -0.26$ (95% CI from -0.486 to -0.005), $p = 0.049$. At stage 2, the success rates were $21/27 = 0.78$ and $18/23 = 0.78$; the difference was -0.005 (95% CI from -0.223 to 0.220), $p = 1.00$.

The mean (SD) reduction in sUr from baseline obtained with allopurinol was 33 (13)% at a dose of 300 mg/day and 49 (14)% at a dose of 600 mg/day. Increasing the allopurinol dose to 600 mg/day for patients above target sUr after stage 1 resulted in an additional sUr decrease of 32 (16)% compared with that produced by the 300 mg/day dose.

For benzbromarone, the reduction in sUr from baseline was 42 (15)% with the 100 mg/day dose and 46 (8)% with the 200 mg/day. Increasing the benzbromarone dose to 200 mg/day in patients above target sUr after stage 1 resulted in an additional sUr decrease of 29 (6)% compared with that produced by the 100 mg/day dose.

DISCUSSION

This study showed that treatment success, defined as reaching sUr ≤ 0.30 mmol/l, by administering allopurinol in patients with cCrCl ≥ 50 ml/min is significantly increased from 29% to 78% by doubling the allopurinol dose to 600 mg/day ($p < 0.001$). Benzbromarone produced significantly greater treatment success at the starting dose (stage 1) than allopurinol, as also shown in previous trials.^{28–29} After dose escalation (stage 2), there was no longer a significant difference in treatment success between the two drugs.

The treatment success rate for allopurinol 300–600 mg/day (78%) was higher than previously reported. Rundles *et al*⁵ found a treatment success rate of 53% (95% CI 29% to 76%) in 19 patients using allopurinol 600 mg. Baseline sUr in these 19 patients (0.56 (0.11) mmol/l) was comparable to that in our study. We may have obtained better results by using a twice-daily dose scheme, in comparison with once daily used by Rundles *et al*, as higher trough oxipurinol concentrations may result in greater xanthine oxidase inhibition. Allopurinol is approved for use up to 900 mg/day,² and even better results may be possible using this maximum dose. In the Netherlands, a national guideline recommends a maximum dose of 700 mg allopurinol/day.³⁰

A treatment duration of 2 months may be considered too short for treatment evaluation, especially in patients with poor renal urate excretion and therefore longer serum urate half-life. In subjects who do not have gout, the serum urate half-life is

Table 2 Efficacy of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day after stage 1 and stage 2*

	Allopurinol	Benzbromarone	p Value
Stage 1 and 2 results	(n = 27)	(n = 23)	
Dose (mg/day)	300–600	100–200	
Treatment goal reached			
sUr ≤0.30 mmol/l	21 (78%)	18 (78%)	1.00
95% CI	59–89%	58–90%	
Treatment goal not reached			
Withdrawn because of ADRs	2 (7%)	3 (13%)	0.62
sUr 0.31–0.36 mmol/l	2 (7%)	2 (9%)	1.00
sUr >0.36 mmol/l	2 (7%)	0 (0%)	0.34
Stage 1 results	(n = 31)	(n = 25)	
Dose (mg/day)	300	100	
Duration (months)	2.3 (0.8)	2.2 (0.7)	0.93
Range	1.5–4.9	1.6–3.2	
Treatment goal reached			
sUr ≤0.30 mmol/l	8 (26%)	13 (52%)	0.049
95% CI	12–45%	33–70%	
Treatment goal not reached			
Withdrawn because of ADRs	2 (7%)	3 (12%)	0.62
sUr 0.31–0.36 mmol/l	12 (39%)	2 (8%)	0.01
sUr >0.36 mmol/l	8 (27%)	7 (28%)	1.00
sUr reached (mmol/l)	0.34 (0.08)	0.29 (0.08)	–
Range	0.21–0.49	0.16–0.45	
ΔsUr from baseline (%)	–33 (13)	–42 (15)	0.04
uUr (mmol/day)	2.2 (1.2)	4.4 (1.7)	<0.001
Range	0.5–6.1	1.5–8.4	
UrCl (ml/min per 1.73 m ²)	3.6 (1.5)	4.9 (2.2)	<0.001
Range	1.0–8.0	3.0–20.6	
Serum oxipurinol (mg/l)	13.1 (10.4)	–	–
Range	3.9–51.3		
Stage 2 results*	(n = 17)	(n = 7)	
Dose (mg/day)	600	200	
Duration (months)	2.5 (0.7)	2.3 (0.8)	0.71
Range	1.5–4.9	1.6–3.2	
sUr reached (mmol/l)	0.27 (0.07)	0.28 (0.04)	–
Range	0.18–0.38	0.23–0.35	
ΔsUr from baseline (%)	–49 (14)	–46 (8)	–
ΔsUr from stage 1 (%)	–32 (16)	–29 (6)	–
uUr (mmol/day)	2.1 (1.0)	4.9 (2.2)	–
Range	1.1–3.5	2.1–8.1	
UrCl (ml/min per 1.73 m ²)	4.3 (1.5)	10.3 (3.7)	–
Range	2.0–6.6	4.6–15.3	
Serum oxipurinol (mg/l)	17.0 (9.9)	–	–
Range	4.9–41.7		

Data are number (%) or mean (SD) and range, unless stated otherwise.

*No statistical comparisons were performed for stage 2 results because of incomparable groups due to selection bias.

ADR, adverse drug reaction; sUr, serum urate concentration; UrCl, urate clearance; uUr, urate excreted in urine.

~0.85 day.³¹ In patients with gout and severe underexcretion of urate (urate clearance 1.5 ml/min; reference value is ~6 ml/min per 1.73 m²), we therefore estimated that the corresponding serum urate half-life is ~4 days. As a steady state is established within five half-lives, a 2-month treatment period should be sufficient for evaluation of allopurinol treatment, even when we take the allopurinol step-up dose scheme into account. In addition, the decrease in sUr obtained with allopurinol 300 mg/day in our study is comparable to that in previous studies using a longer treatment period.³²

Treatment success with benzbromarone was increased from 52% to 78% by titrating the dose up to 200 mg/day (p = 0.075). The success rate was somewhat lower than expected from a previous study, in which we found a 92% success rate with benzbromarone 200 mg/day in 24 patients.⁷ This may be due to

some non-adherent patients because of a difference in trial design (ie, exclusion of patients with low adherence to allopurinol in a subsequent benzbromarone or probenecid treatment group) and a lower tolerability rate. We did not obtain any other data on the sUr-lowering effect and treatment success of benzbromarone 200 mg/day.

Adherence to gout medication has been reported to be low in general.³³ In this study, we measured serum oxipurinol concentrations in the allopurinol group. All patients had measurable serum oxipurinol concentrations, and these increased in each patient for whom the allopurinol dose was increased; reported reference values for allopurinol 300 mg/day are 5–15 mg/l, but higher values may be obtained.^{22–34} Poor adherence by some patients in the benzbromarone group cannot be excluded.

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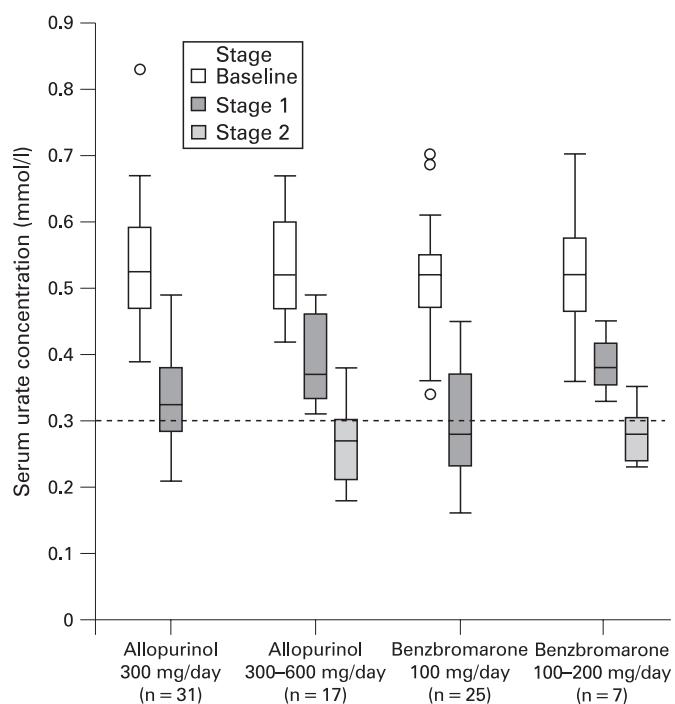


Figure 2 Box plot diagram of serum urate concentrations (sUr) at baseline and after stage 1 and stage 2 treatment with allopurinol and benzbromarone. Results are depicted in two groups for each drug: patients who completed stage 1 treatment and patients who completed stage 2. o, outlying value; dotted line, target sUr.

In this study, all patients had been referred to a rheumatologist, which may have introduced bias to inclusion of patients with more severe gout. Better results may be obtained in patients with less severe gout and lower baseline sUr.

Allopurinol of different (generic) brands was used, which may have increased the variation in results. In the Netherlands, the requirement for bio-equivalence is that the 90% CI must be within 80–125% of the reference value.

The target sUr is still a matter of debate.³⁵ In the recent EULAR recommendations, a less strict target sUr of ≤ 0.36 mmol/l was proposed for gout treatment in general, but, in the case of severe gout, the treatment target may be set lower.¹ With a treatment goal of sUr of ≤ 0.36 mmol/l, treatment successes would be 85% for allopurinol and 87% for benzbromarone.

The tolerability rates found for allopurinol and benzbromarone did not differ significantly from data in other studies. All adverse drug reactions reported for allopurinol and benzbromarone occurred in stage 1, and these reactions have been described previously.^{11–13, 36, 37} Starting sUr-lowering treatment can cause gout flares because of mobilisation of urate related to the rapid decline in sUr. One patient developed generalised exanthema after starting allopurinol at a dose of 100 mg/day, and one patient developed exfoliative dermatitis during stage 1. No hepatitis, defined as grade 2, 3 or 4 liver enzyme increases, was seen with allopurinol or benzbromarone during the study period. Severe hepatotoxicity caused by benzbromarone is seen in rare cases, and has led to withdrawal of benzbromarone in many countries. A mechanism for this hepatotoxicity was recently reported.³⁸ Patients with high renal urate clearances, eg, from using uricosuric drugs, have an increased risk of urate nephrolithiasis. Therefore, benzbromarone is relatively contraindicated in patients with normal renal urate clearances. In our

Table 3 Adverse drug reactions (ADRs) leading to withdrawal and total ADR reported

ADR	Allopurinol (n = 30)	Benzbromarone (n = 25)
Number of patients with ADR	2 (7%)/2 (7%)	3(12%)/5 (20%)
95% CI	1–22%/1–22%	3–31%/7–40%
Type of ADR		
Dizziness and flushing	–/–	1 (4%)/1 (4%)
Gastrointestinal	–/–	2 (8%)/2 (8%)
Hepatitis*	–/–	–/–
Gout flares	–/–	–/1 (4%)
INR increase	–/–	–/1 (4%)
Rash/skin reactions	2 (7%)/2 (7%)	–/–
Severe skin reactions	–/–	–/–

ADRs expressed as ADR leading to withdrawal (n (%))/total ADRs (n (%)) reported; one patient could report more than one ADR.

*Grade 2, 3 or 4 liver enzyme increases.

group of patients receiving benzbromarone, no urate nephropathy, nephrolithiasis or urolithiasis was reported, and no nephropathy was found on calculating creatinine clearances before and after treatment.

This study was conducted in patients with a cCrCl ≥ 50 ml/min. Results cannot be extrapolated to patients with cCrCl < 50 ml/min, because (1) the allopurinol dose should then be adjusted to renal function, and (2) the efficacy of benzbromarone falls gradually with decreasing renal function to inefficacy in the presence of cCrCl < 25 ml/min.³⁹

We used sUr as a surrogate variable for clinical success. Previous studies have found that the sUr attained is inversely related to prevention of recurring gout flares and to the speed of size reduction of tophi.^{15–19} Therefore, sUr is considered an important variable in clinical practice for evaluating the success of sUr-lowering treatment for gout in the long term.

There are few therapeutic options available for lowering sUr to target levels other than the drugs used in this study. The uricosuric drug, sulfinpyrazone, is not widely used because of its adverse effects profile.³⁹ Probenecid was found to be less effective and less well tolerated than benzbromarone.⁷ Febuxostat, a novel xanthine oxidase inhibitor, has been found to be more effective than allopurinol;³² however, the allopurinol dose used for comparison was fixed at 300 mg/day.⁴⁰ On the other hand, febuxostat may prove beneficial in patients with diminished renal function, as it is not renally excreted. A higher allopurinol dose (eg, 600 mg/day) in the above comparative study may have given similar end point results for allopurinol and febuxostat.

Another sUr-lowering drug under development is pegylated uricase, aimed at patients who are unresponsive to current sUr-lowering treatments. As combination therapy of allopurinol and a uricosuric drug (benzbromarone or probenecid) produces additional lowering of sUr, this may also be a beneficial option.⁴¹ The impact of gout on work absence and productivity is substantial, so pharmaco-economic studies on the newer and older (out-of-patent) drugs, such as allopurinol and benzbromarone, are necessary.⁴²

CONCLUSIONS

In patients with gout and renal function defined as cCrCl ≥ 50 ml/min, increasing the allopurinol dose up to 600 mg/day and benzbromarone dose up to 200 mg/day produces greater treatment success (both 78% successful in attaining the target sUr of ≤ 0.30 mmol/l). No significant differences in treatment success were found between allopurinol and benzbromarone

after the dose increase, and the increased dose was well tolerated for both drugs.

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A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout

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