Practice research in the field of gout - clinical pharmacology of antihyperuricemic drugs

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Chapter 3

Outcome research with antihyperuricemic drugs

Chapter 3.1

Biochemical effectiveness of allopurinol and allopurinol-probenecid in previously benzbromarone-treated gout patients

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Abstract

Objectives

In 2003, the uricosuric drug benzbromarone was withdrawn from the market. The first alternative drug of choice was the xanthine oxidase inhibitor allopurinol. The purpose was to investigate (1) the efficacy of allopurinol (standard dosage) compared with previous treatment with benzbromarone; and (2) the combination therapy allopurinol-probenecid as an effective alternative treatment compared with previous benzbromarone treatment.

Methods

A prospective, open study was carried out in a cohort of 51 gout patients who discontinued benzbromarone therapy because of market withdrawal. Patients were given 200-300 mg allopurinol (stage 1). When allopurinol failed to attain the target serum urate (sUr) levels ≤0.30 mmol/l, probenecid 1,000 mg/day was added (stage 2).

Results

Treatment with benzbromarone monotherapy (range: 100-200 mg/day; mean 138 mg/day) resulted in 92% of patients reaching target levels sUr ≤0.30 mmol/l with a decrease of 61% [± 11%] (mean [± standard deviation]) compared to baseline. In stage 1, 32 patients completed treatment with allopurinol monotherapy (range 200-300 mg/day; mean 256 mg/day); this resulted in 25% of patients attaining sUr target levels. Decrease in sUr levels was 36% [± 11%], which was significantly less compared to treatment with benzbromarone ($p<0.001$). In stage 2, 14 patients received allopurinol-probenecid combination therapy, which resulted in 86% of patients attaining target sUr levels (after failure on allopurinol monotherapy), which was comparable to previous treatment with benzbromarone ($p=0.81$). Decrease in sUr levels was 53% [± 9%] ($CI_{95\%}$ 48-58%), which was a non-significant difference compared to previous treatment with benzbromarone ($p=0.23$).

Conclusions

Benzbromarone is a very effective antihyperuricemic drug with 92% success in attainment of target sUr levels ≤0.30 mmol/l. Allopurinol 200-300 mg/day was shown to be a less potent alternative for most selected patients to attain target sUr levels (25% success). In patients failing on allopurinol monotherapy, the addition of probenecid proves to be an effective treatment strategy for attaining sUr target levels (86% success).

Introduction

In 2003, benzbromarone was withdrawn from the European market [1]. The reason for the withdrawal was the risk of fulminant hepatitis according to the information given by the manufacturer. Since the introduction of benzbromarone in the early 1970s, four cases of severe hepatitis have been published [2-5]. On the other hand, benzbromarone seems well tolerated in general use [6] in contrast to allopurinol, which causes frequently (25%) allergic skin reactions. The uncertainty remains whether the efficacy-safety balance of benzbromarone really is unfavourable, compared to the other antihyperuricemic drugs available like allopurinol, probenecid and sulphinpyrazone [7]. In Europe, benzbromarone was available only as a prescription uricosuric drug in a limited number of countries. In the Netherlands, the only licensed alternative for patients with chronic gout was allopurinol, a uricostatic drug acting by inhibition of xanthine oxidase.

The goal of antihyperuricemic treatment is to reduce the serum urate (sUr) level below the threshold of supersaturation to allow the dissolution of existing monosodium urate (MSUr) crystals in the joints and to stop the deposition of new crystals [8-11]. 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 treatment goal of antihyperuricemic therapy is usually supposed to reach sUr levels below 0.36 mmol/l [9-11]. It is shown that recurrent gouty attacks are better prevented [13-14] and that tophi dissolve more quickly [16] in the presence of sUr levels ≤0.30 mmol/l, compared with levels 0.30-0.36 mmol/l. Thus, we aimed the sUr treatment goal for gout patients at ≤0.30 mmol/l.

The amount of urate in the body depends on dietary intake, synthesis and excretion. Hyperuricemia results from the overproduction of urate (10%), from the underexcretion of urate (90%) or often a combination of the two [15]. Therefore, theoretically, the urate balance, in terms of the ratio of overproduction and underexcretion of urate, may be clinically important for the rational choice of a uricostatic drug, a uricosuric drug or a combination of both. However, there are no trials to support or refute this theory [7]. From observational studies, it is concluded that benzbromarone 75-120 mg/day is very effective in the control of hyperuricemia, and better than allopurinol 300-450 mg/day [6, 17-18].

We carried out an observational study to evaluate the effectiveness of allopurinol monotherapy and combination therapy of allopurinol with the uricosuric drug probenecid in underexcretor-type and overproducer-type gout patients previously treated with benzbromarone. Because allopurinol is reported to be less potent than benzbromarone in lowering sUr, we investigated the combination allopurinol-probenecid as an alternative treatment when allopurinol failed.

Methods

Patients and inclusion criteria

A prospective, open label study was carried out in patients who had to discontinue benzbromarone therapy and contacted the rheumatology department in the period July-December 2003. The inclusion criteria were the following: (1) diagnosis of gout proven by presence of MSUr crystals in the synovial fluid [19] or otherwise complying with the American Rheumatism Association criteria [20]; (2) pre-treatment with benzbromarone monotherapy of 100-200 mg/day for at least 2 months with available sUr efficacy results; (3) no relevant liver disease and (4) no relevant renal disease, defined as glomerular filtration rate (GFR) >50 ml/min per 1.73 m^2.

Study design and data collection

Before entering the study, liver function, serum creatinine (sCr), sUr, urinary creatinine excretion (uCr) and urinary urate excretion (uUr) on unrestricted purine diet were measured after benzbromarone was stopped for at least 1 month. GFR was estimated from the simplified Modification of Diet in Renal Disease (MDRD) formula [21]. Underexcretion of urate was defined as a urate clearance (ratio uUr/sUr) <6.0 ml/min per 1.73 m^2 [22]. Results of pre-treatment with benzbromarone were collected from the patient's chart.

In stage 1, patients were given allopurinol with a maximum of 200-300 mg once a day in a step-up dosage scheme; maximum dosage prescribed depended on kidney function, tolerability and prescriber's preference. When the treatment goal of sUr ≤0.30 mmol/l was not reached with allopurinol after 2 months, patients were included in stage 2, and probenecid 500 mg twice daily was added to allopurinol. Each treatment regimen was evaluated after a treatment period of >2 months, and sCr, sUr, uCr and uUr were measured. Prophylaxis of gouty episodes with colchicine was prescribed to all patients until target sUr level was reached (sUr ≤0.30 mmol/l).

Primary endpoints for stages 1 and 2 were the percentages of patients attaining sUr target ≤0.30 mmol/l and the relative decrease in sUr attained with each treatment regimen.

Statistical analyses

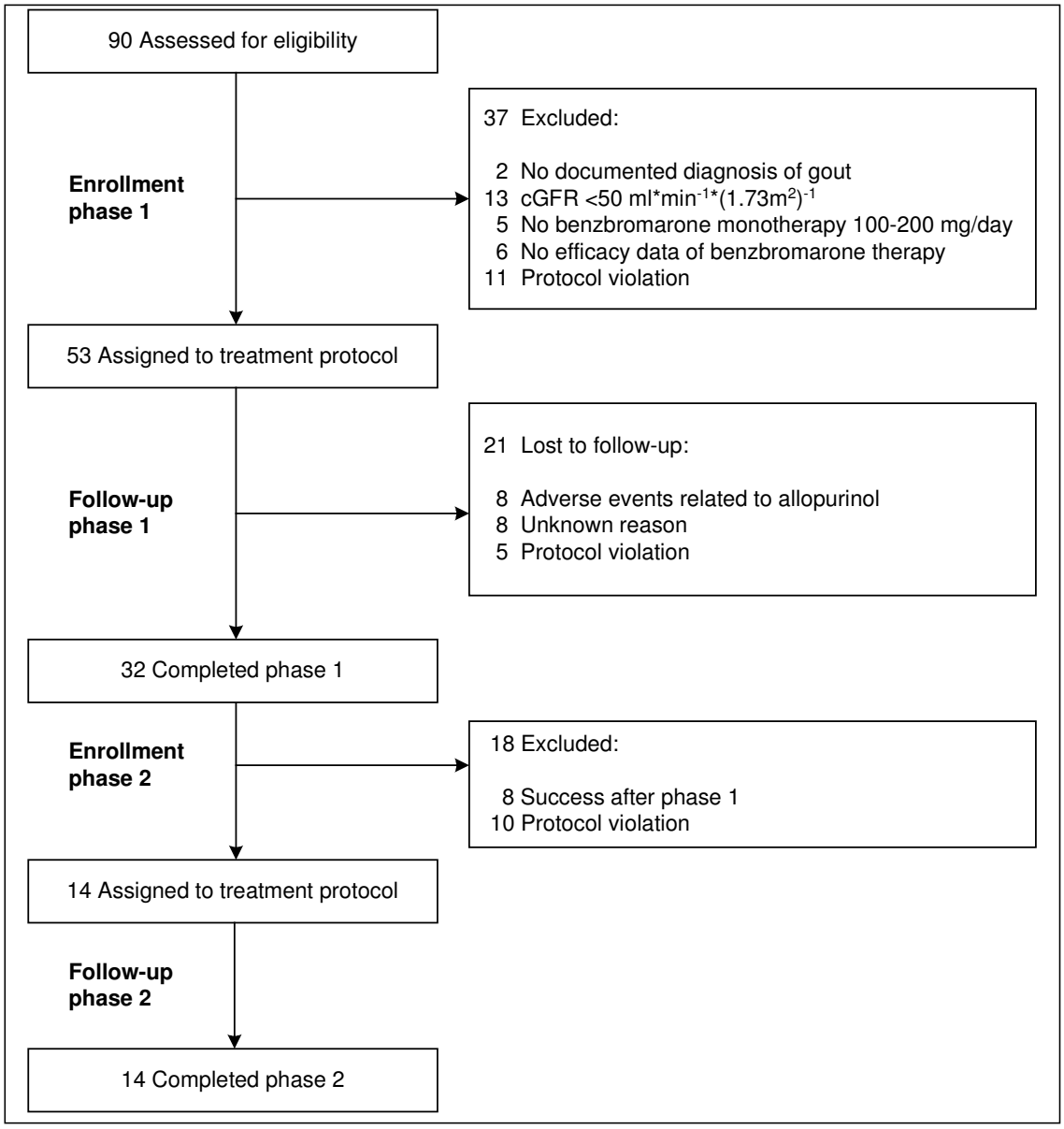
Statistical Package for the Social Sciences (SPSS) 14.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for data collection, data validation, data selection and statistical analysis. Student's two-sided paired t test and chi-squared test were used to compare the effectiveness of benzbromarone, allopurinol and allopurinol-probenecid therapy. Yates's continuity correction was used where appropriate. Normality was verified with Kolmogorov-Smirnov analysis. A p-value <0.05 was considered statistically significant.

Results

Population

Ninety patients made an appointment with the rheumatology department because of benzbromarone withdrawal. Fifty patients (55%) were assigned to stage 1 treatment and received allopurinol 200-300 mg/day, Figure 1. Table 1 shows demographic data, urate results on benzbromarone therapy and urate results at baseline >4 weeks after discontinuation of benzbromarone therapy. Thirty-two patients (64%) completed stage 1 and were included in the analysis. Eight patients attained target serum levels on allopurinol 200-300 mg/day and completed the study. Fourteen patients were assigned to and completed the combination therapy allopurinol-probenecid 500 mg twice daily (stage 2) and were included in the analysis.

Figure 1. Enrolment and assignment of patients to stage 1 and stage 2 treatment



Legend: GFR = Glomerular filtration rate.

Table 1: Demographic data of patients enrolled in stage 1 (allopurinol) and in stage 2 (allopurinol-probenecid)

		Stage 1 Allopurinol (n=52)	Stage 2 Allopurinol-probenecid (n=14)
Demographics			
Age (y)	mean [± SD] range	57 [± 10] 41-84	55 [± 8] 46-74
Male gender		92%	93%
Tophaceous gout		23%	14%
Underexcretor-type		95%	92%
GFR (ml/min per 1.73 m^2)	50-80 >80	54% 46%	50% 50%
History of allopurinol use		20%	14%
Baseline urate characteristics			
Baseline sUr (mmol/l)	mean [± SD] range	0.55 [± 0.08] 0.41-0.69	0.54 [± 0.08] 0.42-0.68
Baseline uUr (mmol/day)	mean [± SD] range	3.7 [± 1.3] 1.6-6.8	3.8 [± 1.7] 1.6-6.8
Baseline UrCl (ml/min)	mean [± SD] range	4.8 [± 1.9] 1.8-11.2	5.0 [± 2.5] 1.8-10.4
Previous benzbromarone results [1]			
Dosage (mg/day)	mean [± SD] range	137 [± 49] 100-200	143 [± 51] 100-200
sUr (mmol/l)	mean [± SD] range	0.21 [± 0.07] 0.09-0.38	0.23 [± 0.06] 0.14-0.31
Decease of sUr	mean [± SD] range	61% [± 11%] 41-76%	58% [± 8%] 48-73%
uUr (mmol/day)	mean [± SD] range	5.0 [± 1.7] 2.4-8.5	5.3 [± 1.7] 2.4-8.0
UrCl (ml/min)	mean [± SD] range	16.1 [± 4.6] 6.2-24.5	16.3 [± 4.9] 6.2-22.2
Treatment goal reached:	sUr ≤0.30 mmol/l sUr ≤0.36 mmol/l	92% 98%	93% 100%

Legend: SD = standard deviation; sUr = serum urate; uUr = urate excreted in urine; UrCl = urate clearance.

[1] Latest results before benzbromarone withdrawal

Biochemical efficacy

Urate results after allopurinol (stage 1) and allopurinol-probenecid (stage 2) treatment are presented in Table 2 and Figure 2. With allopurinol monotherapy, the sUr reached was 0.36 [± 0.07] mmol/l, and eight (25%) patients reached target sUr ≤0.30 mmol/l. Compared to treatment with benzbromarone 100-200 mg/day, significantly less patients attained target sUr levels ($p<0.001$). With allopurinol-probenecid, sUr reached was 0.25 [± 0.04] mmol/l, and 12 (86%) patients reached target sUr after failure on allopurinol monotherapy. No significant difference was found compared to treatment with benzbromarone ($p=0.81$).

Using allopurinol monotherapy, sUr decreased 36% [± 11%] compared to baseline. This was significantly less than relative sUr decrease attained with benzbromarone in this group ($p<0.001$). With allopurinol-probenecid treatment, sUr decreased 53% [± 9%] ($CI_{95\%}$ 48-58%), which did not significantly differ from benzbromarone ($p=0.23$).

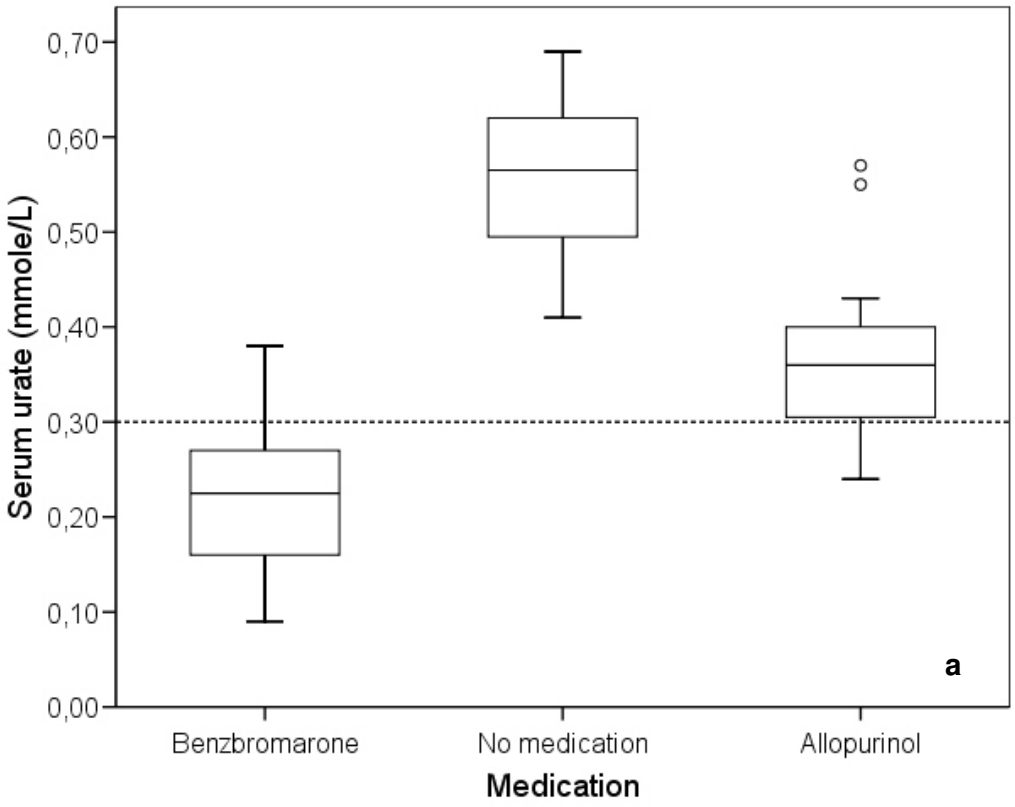
Figure 3 shows cumulative probability plots of target sUr selected and percentage of treatment success found in stages 1 and 2 for selected target sUr and different treatment regimens.

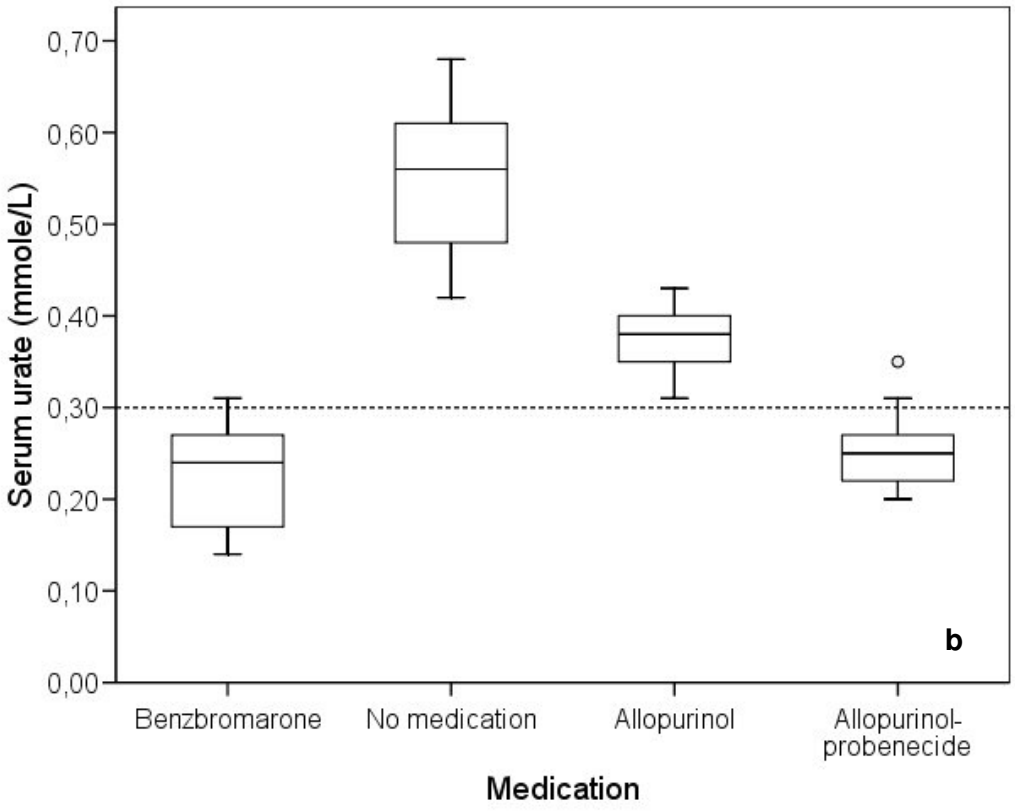
Table 2. Effectiveness of allopurinol (stage 1) and allopurinol-probenecid combination therapy (stage 2)

		Stage 1 Allopurinol (n=32)	Stage 2 Allopurinol-probenecid (n=14)
Dosage allopurinol (mg/day)	mean [± SD] range	256 [± 50] 200-300	243 [± 51] 200-300
Dosage probenecid (mg/day)		-	1,000
sUr reached (mmol/l)	mean [± SD] range	0.36 [± 0.07] 0.24-0.57	0.25 [± 0.04] 0.20-0.35
Decrease of sUr	from baseline from allopurinol from benzbromarone	–36% [± 11%] - +78% [± 60%]	–53% [± 9%] –33% [± 10%] +19% [± 43%]
uUr (mmol/day)	mean [± SD] range	2.3 [± 0.8] 0.8-4.3	3.1 [± 0.9] 1.5-4.4
UrCl (ml/min)	mean [± SD] range	4.4 [± 1.3] 2.3-7.7	8.8 [± 2.4] 4.5-13.9
Treatment goal reached:	sUr ≤0.30 mmol/l sUr ≤0.36 mmol/l	25% 53%	86% 100%

Legend: sUr = serum urate; uUr = urate excreted in urine; UrCl = urate clearance.

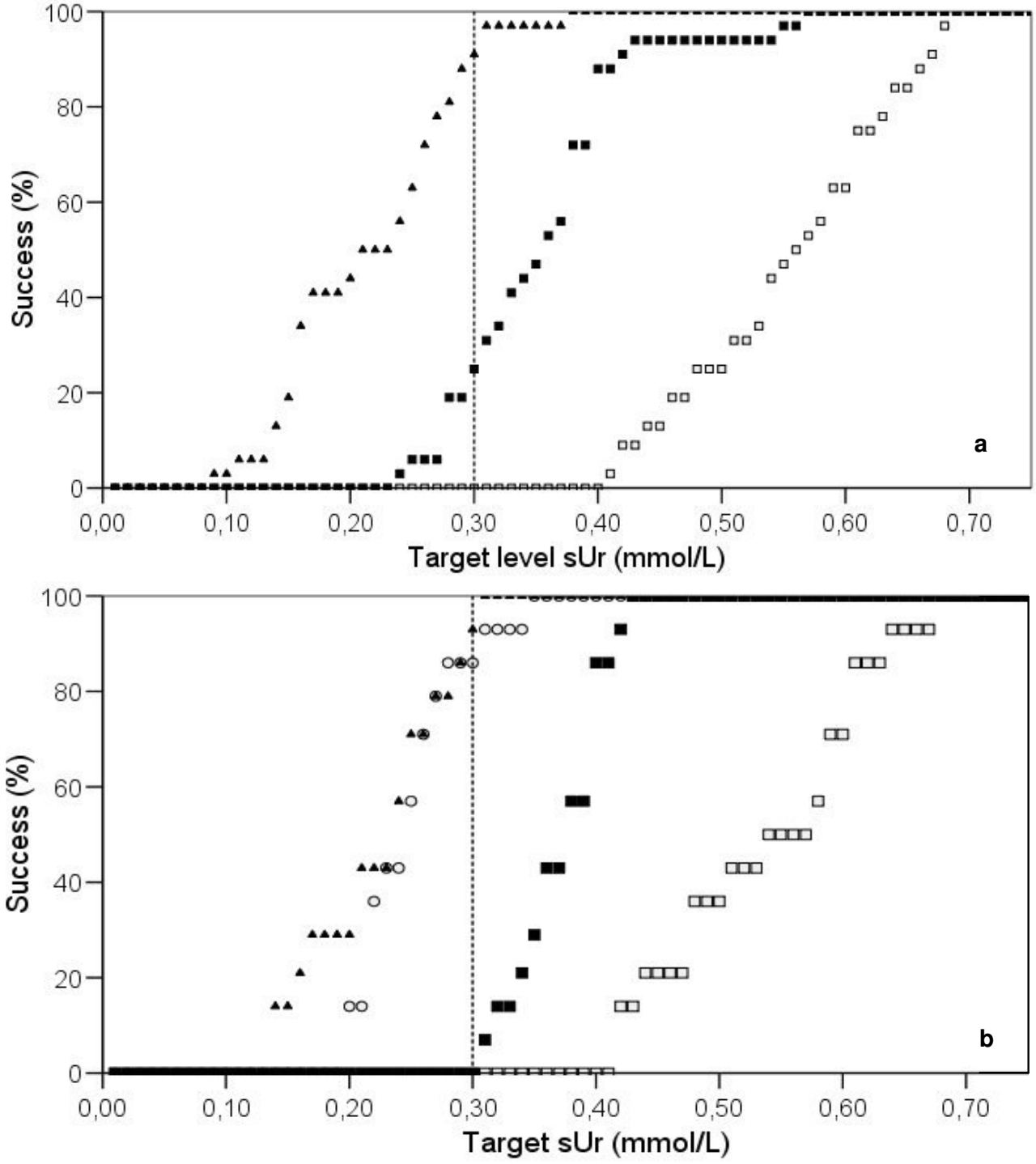
Figure 2. Box-plot diagram for sUr results of (a) stage 1, n=32; (b) stage 2, n=14.





Legend: o = outlying value.

Figure 3. Cumulative probability plot of variable target sUr concentrations and treatment success of target sUr for (a) stage 1, n = 32 (b) stage 2, n=14.



Legend: ▲ = benzbromarone, ■ = allopurinol, o = allopurinol-probenecid, □ = no medication; sUr = serum urate concentration.

Discussion

First, this study shows that benzbromarone is a very potent antihyperuricemic drug; in this cohort of patients using benzbromarone 100-200 mg/day, more than 90% of the patients have optimal sUr levels. With allopurinol standard dosage 200-300 mg/day, comparable effectiveness cannot be achieved for this group. The average allopurinol dosage (mean 243 mg/day) might be considered relatively low; however, (1) no efficacy data on allopurinol ≥600 mg/day are available in the literature; (2) dosages >300 mg/day are generally not advised because of increased risk of adverse drug reactions [23]; (3) benzbromarone (mean 138 mg/day) and probenecid (1,000 mg/day) could also be dosed higher.

It must be noted that every patient in this study was previously treated with benzbromarone, thereby introducing the possibility to overestimate the percentage of responders to benzbromarone. Furthermore, a dropout occurred in stage 1 of 38%, which may have influenced the outcome. The relatively high dropout rate was mainly due to the design of the study (cohort) in combination with the sudden need for alternative treatment. On the other hand, we found a mean relative decrease in sUr of 61% for benzbromarone and 36% for allopurinol, which corresponds well with values published in the literature of 54-58% for benzbromarone 80-125 mg/day and 27-44% for allopurinol 300 mg/day in patients that were not previously treated with benzbromarone [6, 17-18, 24-25].

This cohort consisted of more than 90% patients of uric acid underexcretor type. From a pathogenic point of view, it is suggested that allopurinol, as an inhibitor of uric acid production, would be more effective in overproducer-type gout. However, this is not supported by clinical data [17]. Previous findings indicate that even in patients with apparently high uUr, a relative underexcretion of urate is present [26]. Thus, when treatment goals are not achieved with allopurinol in this group of patients, combination with a uricosuric drug (e.g. benzbromarone, probenecid) might be very useful.

Adding probenecid to allopurinol contributed an additional 33% [± 10%] ($CI_{95\%}$ 28-38%) decrease in sUr on average, resulting in reaching the target sUr for most patients (87% success). Thus, in finding an appropriate alternative therapy for benzbromarone, adding probenecid to allopurinol was proven an effective strategy. An interaction between allopurinol and probenecid is described in the literature [15], resulting in an increased clearance of oxipurinol, the active metabolite of allopurinol. However, our data do not support this finding to be clinically important, as the addition of probenecid to allopurinol decreased sUr with 31% on average.

In stage 1, five patients (10%) stopped allopurinol therapy because of adverse events related to allopurinol. Reported events were rash, pruritus, diarrhoea, nausea and dizziness, which are all well known side effects of allopurinol. Becker *et al.* [24] found a similar rate (12%) of adverse events related to allopurinol.

There are few therapeutic options available to lower sUr to target levels other than the drugs used in this study. The uricosuric drug sulphinpyrazone is not widely used due to its adverse

effects profile [27]. Minor additive serum-lowering effects may be achieved by losartan or fenofibrate [27-28]. The uricostatic febuxostat may be available soon. Recently, it was shown that when using febuxostat 80-120 mg/day, 47-66% of the patients reached sUr levels ≤0.30 mmol/l compared to 13% with allopurinol 300 mg/day [24]. A new promising treatment option for patients with severe tophaceous gout is the development of recombinant uricase [29-30] and pegylated recombinant uricase. Uricase-based drugs are potentially very effective but also very expensive drugs, so further (pharmaco-economic) studies on optimizing antihyperuricemic antihyperuricemic therapy with old (out of patent) drugs, like benzbromarone, are warranted. At this moment, benzbromarone seems to be the most effective antihyperuricemic drug, and from our point of view, availability of benzbromarone in other countries would make treatment of difficult gout more successful [31].

Conclusion

Benzbromarone is a very effective antihyperuricemic drug with 91% success in attainment of target sUr levels ≤0.30 mmol/l. Allopurinol 200-300 mg/day was shown to be a less potent alternative for most selected patients to attain target sUr levels (25% success). In patients failing on allopurinol monotherapy, the addition of probenecid proves to be an effective treatment strategy for attaining sUr target levels (86% success).

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Chapter 3.2

Efficacy and tolerability of urate lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol

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Abstract

Objectives

The purpose of this study was to investigate the efficacy and tolerability of allopurinol as the first-choice antihyperuricemic treatment for gout, and compare the efficacy and tolerability of benzbromarone and probenecid as second-choice treatment.

Methods

Prospective, multi-centre, open-label, two-stage, randomised controlled trial in gout patients with normal renal function. Enrolled patients were given 300 mg allopurinol for 2 months (stage 1). Those patients who could not tolerate allopurinol or who did not attain the target serum urate concentration (sUr) ≤0.30 mmol/l (5.0 mg/dl), which was defined as successful, were randomised to benzbromarone 200 mg/day or probenecid 2,000 mg/day for another 2 months (stage 2).

Results

Ninety-six patients were enrolled in stage 1. Eighty-two patients (85%) were eligible for analysis at the end of stage 1. There was a mean [± SD] decrease in sUr concentration of 35% [± 11%] from baseline; 20 patients (24%) attained target sUr (0.30 mmol/l); and 9 patients (11%) stopped allopurinol because of adverse drug reactions.

Sixty-two patients were enrolled in stage 2: 27 patients received benzbromarone (with 3 excluded from analysis) and 35 received probenecid (with 4 excluded from analysis). Treatment with benzbromarone was successful in 22/24 patients (92%) and with probenecid in 20/31 patients (65%) ($p=0.03$ compared with benzbromarone). Compared with baseline values, a mean [± SD] decrease of sUr concentration of 64% [± 9%] occurred with benzbromarone and 50% [± 7%] with probenecid ($p<0.001$).

Conclusion

This study showed that allopurinol 300 mg/day has a poor efficacy and tolerability profile when used to attain a biochemical predefined target level of sUr ≤0.30 mmol/l, following 2 months of treatment. In stage 2, benzbromarone 200 mg/day was more effective and better tolerated than probenecid 2,000 mg/day. Trial registration number: ISRCTN21473387.

Introduction

Allopurinol is the drug of choice for long-term urate lowering therapy in the 2006 European League Against Rheumatism (EULAR) evidence-based recommendations for gout. Uricosuric agents such as probenecid and sulfinpyrazone can be used as alternatives, and benzbromarone is only recommended in patients with mild to moderate renal insufficiency. Given the scarce clinical trial data, it remains questionable whether the efficacy-safety balance of benzbromarone and probenecid is unfavourable compared with the first-choice treatment, allopurinol [1].

Since the introduction of benzbromarone in the early 1970s, four cases of severe hepatitis have been published [2-5]. Benzbromarone, however, seems well tolerated in general use [6]. In contrast, allopurinol rather frequently causes allergic skin reactions (2-5%), and in rare cases causes even a life-threatening hypersensitivity syndrome [7-11]. In Europe, benzbromarone used to be available as a prescription drug in a limited number of countries. In the Netherlands, the only alternative in chronic gout was allopurinol. When allopurinol treatment was unsuccessful, the uricosuric drug probenecid was available for restricted use. Benzbromarone was withdrawn from the market in Europe in 2003, but was licensed again in some countries in 2004 [12]. Its use is now restricted for patients with gout who are allergic to allopurinol or those in whom allopurinol is contra-indicated.

The goal of antihyperuricemic treatment is to reduce the serum urate (sUr) level below the threshold of supersaturation to prevent any gouty attack by allowing the dissolution of existing monosodium urate (MSUr) crystals in the joints and to prevent the deposition of new crystals in cases of severe tophaceous accumulation [9-11]. 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].

According to the EULAR recommendations, the treatment goal of antihyperuricemic lowering therapy is to reach target serum urate levels below 0.36 mmol/l (6.1 mg/dl) [13]. Recurrent gouty attacks are better prevented and tophi dissolve more quickly with target serum urate concentrations below 0.30 mmol/l (5.0 mg/dl) rather than 0.30-0.36 mmol/l [14-18]. The British Guideline (2007) sets the sUr treatment goal for gout patients at ≤0.30 mmol/l [19].

With the aim of collecting more evidence-based data, in the present study we: (1) investigated the efficacy and tolerability of allopurinol as first-choice sUr-lowering treatment for gout; (2) compared the above with the efficacy and tolerability of benzbromarone and probenecid as second-choice treatments.

Methods

Patients and inclusion criteria

This prospective, multi-centre, open label, randomised controlled trial was carried out in patients recently diagnosed with gout by a rheumatologist. Eligibility criteria were [20-23]: (1) a diagnosis of gout confirmed by microscopic evidence of urate crystals or complying with the American Rheumatology Association (ARA) criteria otherwise; (2) no history of use of one of the study drugs; (3) no relevant liver disease; (4) no relevant renal disease - defined as calculated creatinine clearance (cCrCl) ≥50 ml/min, using the Cockcroft and Gault formula; and (5) an indication for antihyperuricemic therapy - presence of tophi or frequent attacks (≥2/year). Before a patient was entered the study, we measured their liver function, serum creatinine (sCr), sUr, urinary creatinine excretion (uCr), and urinary urate excretion (uUr) on unrestricted purine diet. Underexcretion of urate was defined as urate clearance (UrCl) <6.0 ml/min per 1.73 m^2 [24]. Urate clearance was calculated by urinary volume (ml/min) * urinary urate concentration / sUr and normalised for a body surface area of 1.73 m^2. Overproduction of urate was defined as uUr >6.0 mmol/day. Normal excretion of urate was defined as UrCl ≥6.0 ml/min per 1.73 m^2 and uUr ≤6.0 mmol/day.

At the time of inclusion in the study, patients were assigned an inclusion number by the rheumatologist (blinded), and consequently randomised to stage 2 treatment. A computer-generated central randomisation schedule with a block size of six was used. The period of study recruitment and follow-up was from June 2005 until January 2007.

Study design and data collection

In stage 1, patients were given allopurinol 300 mg once daily in a step-up dosage scheme (100-200-300 mg/day, with the dose increased every week), which is a common fixed-dose regimen used in clinical practice in Europe and in other gout studies [13, 25-27]. When allopurinol was not tolerated or when the treatment goal of sUr ≤0.30 mmol/l was not reached after 2 months, patients were switched to stage 2 treatment: benzbromarone 200 mg once daily (Desuric®; OTL Pharma, Breda, The Netherlands) - step-up 100-200 mg/day, dose increased after 1 week - or probenecid 1,000 mg twice daily (Probenecid Weimer®; Biokanol Pharma, Rastatt, Germany) - step-up 500-1,000 mg twice daily, dose increased after 1 week.

Defined daily doses are allopurinol 400 mg/day, benzbromarone 100 mg/day and probenecid 1,000 mg/day. We used a fixed dosage in the upper dosage range of benzbromarone and probenecid, because (1) adequate treatment of patients refractory to allopurinol (standard) treatment was warranted, and (2) benzbromarone 200 mg/day had not been tested in a clinical controlled trial before. Colchicine 0.5-1 mg/day was prescribed fot prophylaxis of gouty episodes, until target sUr level was reached (sUr ≤0.30 mmol/l); when colchicine was not tolerated, a non-steroidal anti-inflammatory drug was prescribed.

Each treatment regimen was evaluated after a treatment period of 2 months by measuring sCr, sUr, uCr and uUr. To evaluate patient adherence for allopurinol, we measured the serum

oxipurinol level by using a validated high-pressure liquid chromatography with ultraviolet detector (HPLC-UV) method [28]. Patients with serum oxipurinol concentrations below the lower limit of quantification (<1.0 mg/l) were excluded from the analysis.

The primary endpoint for stages 1 and 2 was the percentage of patients tolerating the antihyperuricemic medication and attaining an sUr concentration below 0.30 mmol/l. Our secondary end point was the relative decrease of sUr concentration attained with each treatment regimen.

The study was approved by the medical ethical committees of both centres and informed consent was obtained from all participating patients.

Statistics

A power calculation indicated that at least 29 evaluable patients were needed in each treatment arm in stage 2 to prove a statistically significant difference between benzbromarone and probenecid (based on an estimated 90% success rate for benzbromarone versus 60% for probenecid, α=0.05, β=0.20) [29]. We expected a success percentage of 20% with allopurinol and a loss to follow-up of 25%, rendering 96 patients for the study.

SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) was used for data collection, data validation, data selection, and statistical analysis. The Student two-sided t-test and Fisher exact test were used to compare the effectiveness of benzbromarone and probenecid; 95%-confidence intervals of proportions were calculated using binomial distribution. Normality was verified with Kolmogorov-Smirnov analysis. A p-value <0.05 was considered statistically significant.

Results

We enrolled 96 patients in stage 1 (Figure 1). Three patients did not fulfil the inclusion criteria because of an estimated CrCl <50 ml/min (protocol violation), leaving ninety-three patients for analysis of baseline characteristics (Table 1). Of these, 82 patients (88%) were eligible for analysis of stage 1; five patients were lost to follow-up and six patients were excluded because of poor adherence based on non-measurable serum oxipurinol levels.

Results of stages 1 and 2 are presented in Table 2 and Figure 2. The treatment was successful in 20 patients (24%), defined as tolerance of allopurinol and attainment of target sUr concentrations (≤0.30 mmol/l). Nine patients (11%) stopped taking allopurinol because of adverse drug reactions (ADRs) (Table 3). In stage 1, the mean [± SD] decrease in sUr concentration with allopurinol was 35% [± 11%]. The mean serum oxipurinol concentration measured was 13.2 [± 7.1] mg/l. Of patients whose sUr concentrations did not reach ≤0.30 mmol/l, 92% had serum oxipurinol concentrations >5.0 mg/l.

Sixty-two patients entered stage 2 of the study: 27 patients received benzbromarone (with 3 excluded from analysis), and 35 received probenecid (with 4 excluded from analysis). In the benzbromarone group, 22/24 patients (92%) were treated successfully in terms of tolerance of study medication and attainment of target sUr concentrations. In the probenecid group, 20/31

patients (65%) were treated successfully, which was significantly less than the treatment success attained with benzbromarone (p=0.026). The success ratio benzbromarone:probenecid was 1.42 ($CI_{95\%}$ 1.07-1.89). With benzbromarone 200 mg/day, the sUr concentration decreased by a mean [± SD] of 64% [± 9%] compared with a decrease of 50% [± 7%] with probenecid 2,000 mg/day (p<0.001).

Figure 1. Flow of participants through each stage of the study

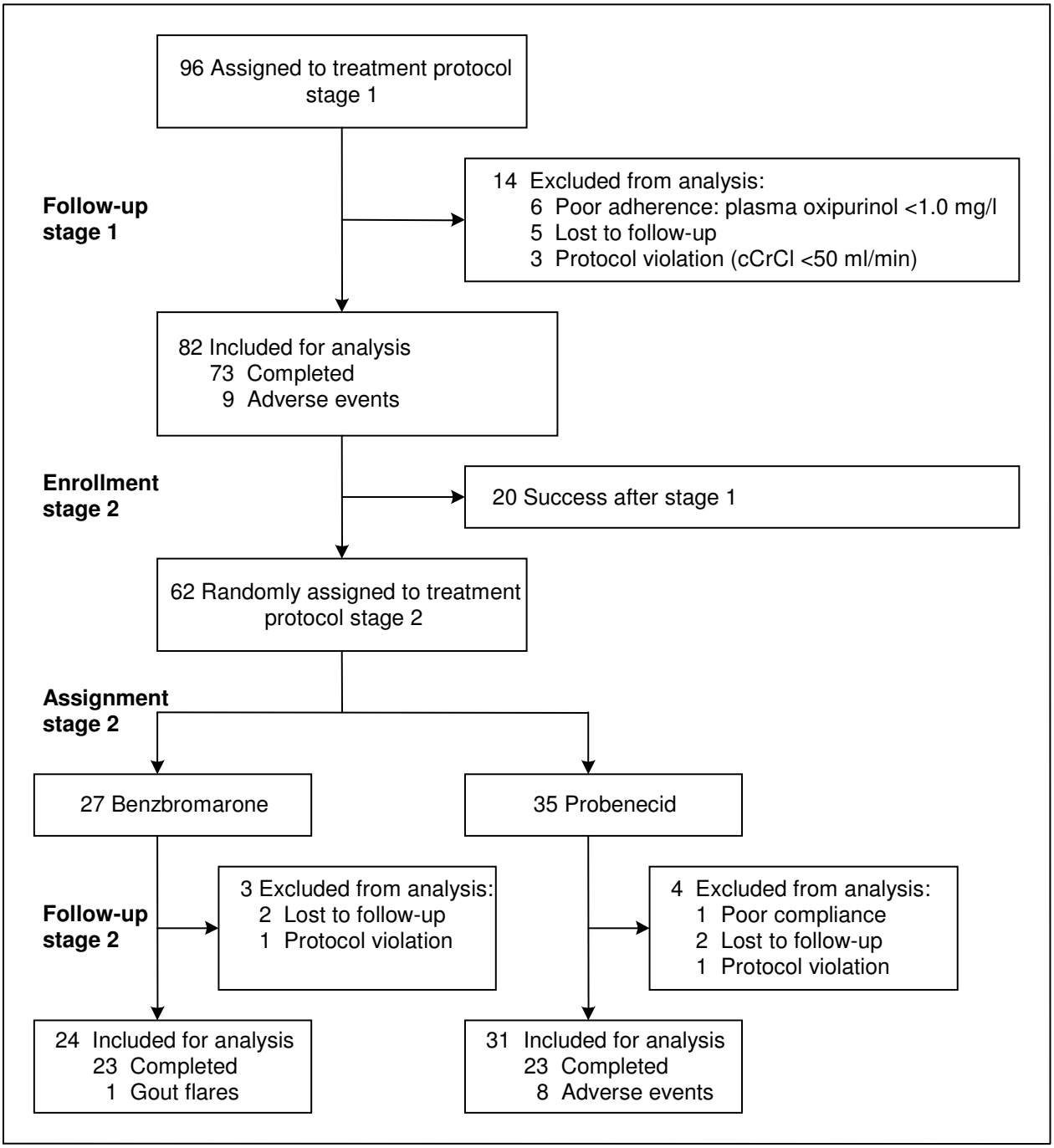


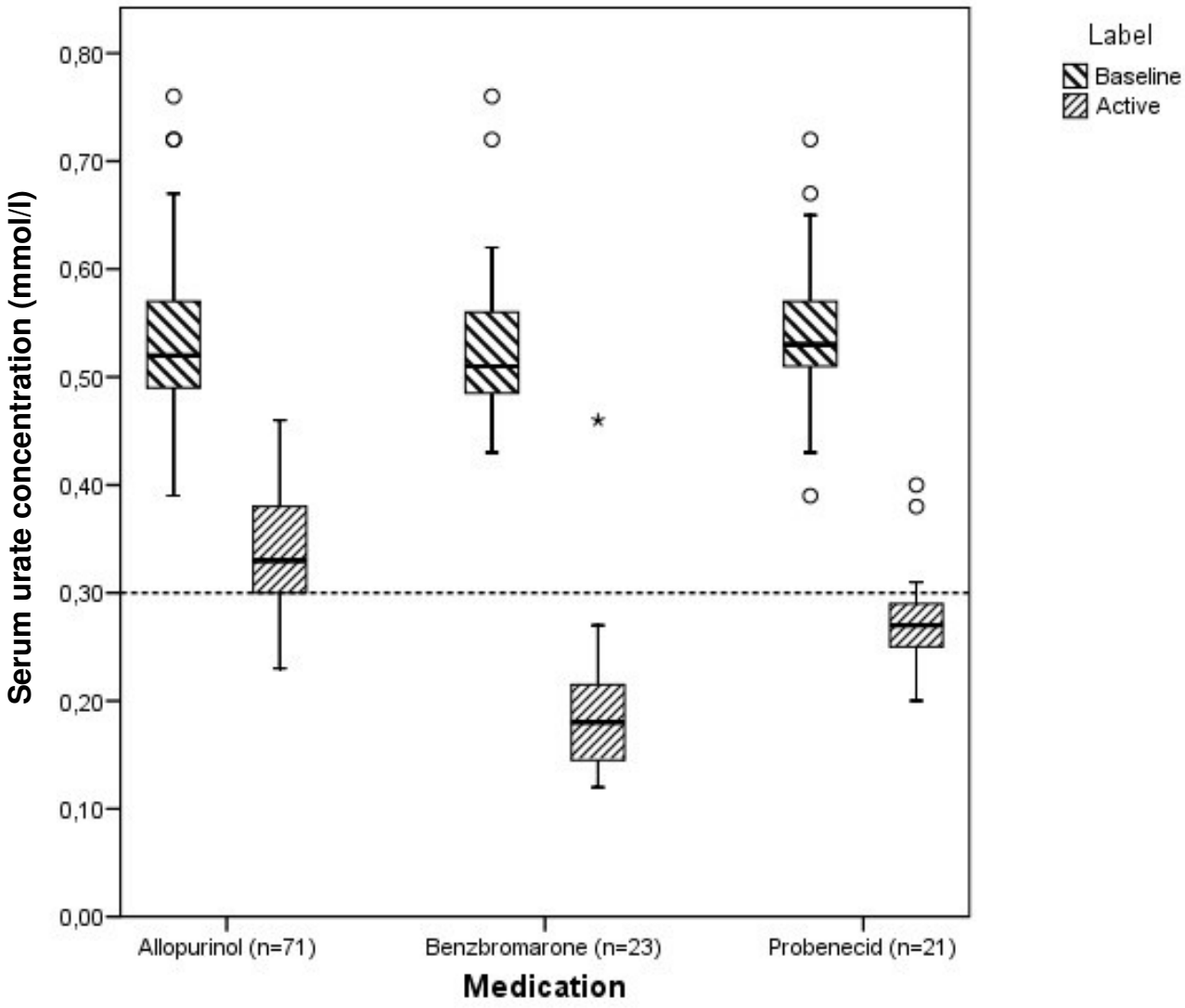
Table 1. Demographic and clinical characteristics of patients

		Stage 1	Stage 2		
		Allopurinol (n=96)	Benzbromarone (n=27)	Probenecid (n=35)	p-value [1]
Demographics					
Age (y)	mean [± SD] range	58 [± 14] 29-86	55 [± 16] 29-86	58 [± 12] 32-77	NS
Male gender		92%	100%	94%	NS
Tophaceous gout		41%	30%	54%	NS
Frequency of gout flares at baseline:	0-2/y 3-5/y >5/y	40% 33% 27%	38% 29% 33%	45% 34% 21%	NS
Body mass index (kg/m^2)	mean [± SD] range	29.3 [± 4.6] 19.4-48.9	29.6 [± 3.4] 24.8-39.2	29.4 [± 3.8] 21.3-36.3	NS
Creatinine clearance (ml/min)	30-50 50-80 >80	3% 32% 65%	- 27% 73%	- 36% 64%	- NS NS
Centre:	Leeuwarden Enschede	52% 48%	52% 48%	46% 54%	NS NS
Urate characteristics at baseline					
sUr (mmol/l)	mean [± SD] range	0.53 [± 0.07] 0.39-0.76	0.55 [± 0.09] 0.43-0.76	0.54 [± 0.07] 0.39-0.72	NS
uUr (mmol/day)	mean [± SD] range	3.6 [± 1.6] 1.2-10.0	4.1 [± 1.8] 2.2-9.8	3.4 [± 1.6] 1.3-10.0	NS
UrCl (ml/min per 1.73 m^2)	mean [± SD] range	3.8 [± 1.7] 1.4-10.4	4.4 [± 1.9] 1.4-7.9	3.6 [± 1.8] 1.5-10.4	NS
Excretor-type	underexcretor normal excretor overproducer	89% 5% 6%	78% 13% 9%	94% 3% 3%	NS NS NS

Legend: NS = non-significant (p>0.05); SD = standard deviation; sUr = serum urate; uUr = urate excreted in urine; UrCl = urate clearance; y = year(s).

[1] Comparison of stage 2 groups.

Figure 2. Box-plot for serum urate concentration (sUr) results of stage 1 and stage 2 antihyperuricemic medication.



Legend: o and * = outlying value; dotted line = target sUr

Table 2. Efficacy of allopurinol as first-line sUr lowering treatment (stage 1) and benzbromarone versus probenecid as second-line treatment (stage 2).

		Stage 1	Stage 2		
		Allopurinol 300 mg/day	Benzbromarone 200 mg/day	Probenecid 2,000 mg/day	p-value [2]
Treatment success results		(n=82)	(n=24)	(n=31)	
Treatment goal reached (sUr ≤0.30 mmol/l)	$CI_{95\%}$	20 (24%) 16%-35%	22 (92%) 73%-99%	20 (65%) 45%-81%	0.026
Treatment goal not reached:					
withdrawn due to ADR		9 (11%)	1 (4%)	8 (26%)	
sUr 0.31-0.36 mmol/l		26 (32%)	0 (0%)	1 (3%)	
sUr >0.36 mmol/l		27 (33%)	1 (4%)	2 (6%)	
Urate results		(n=73)	(n=23)	(n=23)	
sUr reached (mmol/l)	mean [± SD] range	0.34 [± 0.06] 0.23-0.46	0.19 [± 0.07] 0.12-0.46	0.27 [± 0.05] 0.20-0.40	<0.001
sUr decrease from baseline		35 [± 11] %	64 [± 9] %	50 [± 7] %	<0.001
uUr (mmol/day)	mean [± SD] range	2.2 [± 1.2] 0.8-6.6	5.3 [± 1.9] 2.6-9.3	4.7 [± 1.7] 0.5-8.1	NS
UrCl (ml/min/1.73m^2)	mean [± SD] range	3.6 [± 1.8] 1.3-7.3	17.7 [± 7.2] 6.7-33.4	10.1 [± 4.5] 1.2-23.2	<0.001
Drug serum concentrations					
Serum oxipurinol (mg/l)	mean [± SD] range	13.2 [± 7.1] 2.5-39.2	-	-	-

Legend: $CI_{95\%}$ = 95% confidence interval; NS = non-significant (p>0.05); sUr = serum urate; uUr = urate excreted in urine; UrCl = urate clearance. ADR = adverse drug reaction

[1] Comparison of stage 2 groups.

Table 3. Reported adverse drug reactions (ADRs): leading to withdrawal, and total ADRs. [1]

	Stage 1	Stage 2	
	Allopurinol (n=82)	**Benzbromarone (n=24)**	**Probenecid (n=31)**
Number of patients with ADRs	9 (11%) / 18 (22%)	1 (4%) / 5 (20%)	8 (26%) / 12 (39%)
$CI_{95\%}$	5-20% / 14-32%	0-19% / 6-38%	12-45% / 22-58%
Type of ADR			
Dizziness	- / -	- / -	1 (3%) / 2 (6%)
Fatigue	1 (1%) / 1 (1%)	- / -	3 (10%) / 3 (10%)
Gastro-intestinal	1 (1%) / 6 (7%)	- / 3 (12%)	5 (16%) / 7 (23%)
Gout flares [2]	- / 2 (2%)	1 (4%) / 2 (8%)	- / 1 (3%)
Headache	- / -	- / -	1 (3%) / 2 (6%)
Muscle pain/cramps	- / 3 (4%)	- / -	- / -
Rash	6 (7%) / 6 (7%)	- / -	1 (3%) / 1 (3%)
Flushing	- / 1 (1%)	- / -	1 (3%) / 2 (6%)
Vision disorder	1 (1%) / 1 (1%)	- / -	- / -

Legend: $CI_{95\%}$ = 95% confidence interval;

[1] ADRs expressed as ADR leading to withdrawal (n(%)) / total ADR (n(%)) reported; every patient could report >1 ADR.

[2] Gout flares might be caused by starting sUr lowering therapy due to mobilisation of urate related to rapid decline of sUr.

Discussion

This study shows that allopurinol 300 mg/day has a poor efficacy and tolerability profile in patients with normal renal function at 2 months of follow-up. With a treatment target sUr concentration of ≤0.30 mmol/l, 24% of patients were treated successfully with allopurinol 300 mg/day. The target sUr concentration is still being debated [31]. In the recent EULAR recommendations a more conservative target sUr concentration of ≤0.36 mmol/l is proposed for gout treatment in general, whereas in patients with severe gout the treatment target might be lower [13]. If we had set a target of ≤0.36 mmol/l in the present study, we would have achieved a treatment success of 56% using allopurinol 300 mg/day. A higher success rate with allopurinol 300 mg/day might be achieved in patients with less severe gout who have a lower baseline sUr, and in overproducer-type patients.

The limited efficacy and modest antihyperuricemic effect of allopurinol with the recommended dose of 300 mg/day is consistent with previous findings [25-27, 29]. Recent guidelines recommend increasing the allopurinol dosage, when necessary, until the target sUr is attained,

with a licensed maximum dosage of 900 mg/day [13, 19]. However, switching to a uricosuric therapy might be preferable, because of several reasons. First, considering that steady state serum urate concentrations depend on the mass balance (difference between input and output) of urate in the body, the sUr-lowering potential of xanthine oxidase inhibitors is limited compared to uricosurics, especially in underexcretor-type gout patients with a mean uUr of 2.2 mmol/day. Second, uncertainty exists about the efficacy-safety balance of higher doses of allopurinol. Lastly, in routine clinical practice and in virtually all clinical research, the commonly used dosage is 300 mg/day. In one case-series, 19 gout patients were treated with allopurinol 600 mg/day: serum urate concentrations decreased with a mean [± SD] of 44% [± 13%], and 10 (52%) patients attained the target level serum urate concentration ≤0.30 mmol/l [32]. No evidence exists for a direct relationship between allopurinol or oxipurinol concentrations and the occurrence of adverse effects in patients with normal renal function [33]. On the other hand, in patients with renal insufficiency, accumulation of oxipurinol is considered a crucial factor in the development of allopurinol hypersensitivity syndrome, which leads to tissue damage by toxic, immunological and/or genetic mechanisms [34-37].

In our study, 11% did not tolerate allopurinol (Table 3). This is slightly more than rates reported in literature, but these differences are probably not significant [13, 32, 38]. The ADRs leading to withdrawal in this study are documented in the literature, except for fatigue [39].

We measured the serum oxipurinol levels to verify adherence to allopurinol. Patients with undetectable oxipurinol concentrations (<1.0 mg/l) were excluded from the analysis. The reported reference range for allopurinol 300 mg/day is 5.0-15 oxipurinol mg/l [40]. Most of the patients who did not attain the target treatment goal had serum oxipurinol concentration >5.0 mg/l (92%). This indicates that these patients were compliant with taking allopurinol treatment. For the purpose of therapeutic drug monitoring of allopurinol therapy, validaton of the proposed therapeutic reference values of serum oxipurinol is needed.

In stage 2, we compared benzbromarone 200 mg/day and probenecid 2,000 mg/day. The results showed that significantly more patients attain target sUr concentrations with benzbromarone. The sUr lowering effects of benzbromarone and probenecid are consistent with previous findings [25-28, 30, 41]. The ADRs reported with probenecid (Table 3) are common side effects of this drug [42].

This study was conducted in patients with a cCrCl ≥50 ml/min. The results cannot be extrapolated to patients with renal insufficiency, because of several reasons (1) allopurinol dosage should be adjusted; (2) benzbromarone is considered ineffective in patients with cCrCl <25 ml/min; and (3) probenecid is considered ineffective in patients with cCrCl <50 ml/min [38].

We used sUr as a surrogate parameter for clinical success. Previous studies have shown that the attained sUr is inversely related to prevention of recurring gout flares and to velocity of size reduction of tophi [12-16]. Therefore, in clinical practice sUr is a well-established parameter for evaluating success of antihyperuricemic therapy for gout in the long-term.

More than 90% of the patients in our study were underexcretors of uric acid. From a pathogenic point of view, it has been suggested that allopurinol, as an inhibitor of uric acid production, is more effective in overproducer-type gout patients. However, this view is not supported by clinical data. Previous findings indicate that even patients with apparently high uUr relatively underexcrete urate [43]. When treatment goals are not achieved with allopurinol in overproducers, combination with a uricosuric drug (e.g. benzbromarone, probenecid) might be useful, considering the (relative) contra-indication of uricosuric drugs for patients with urinary urate excretion >4.2 mmol/day [29].

Besides the drugs used in this study, there are few therapeutic options available to lower sUr to target concentrations. The uricosuric drug sulfinpyrazone is not widely used due to its adverse effect profile [38]. In a recent study, 47-66% of patients taking febuxostat 80-120 mg/day reached sUr concentrations below 0.30 mmol/l compared with only 13% who were taking allopurinol 300 mg/day [25]. A new treatment option for patients with severe tophaceous gout, recombinant uricase and pegylated recombinant uricase, seems promising [29-47]. In short-term studies, uricase-based drugs have been effective but they are expensive drugs. The impact of gout on absence from and productivity is substantial, so pharmaco-economic studies are necessary, comparing the newer and older (out of patent) drugs, such as allopurinol and benzbromarone [48].

It seems that benzbromarone is a highly efficacious oral sUr-lowering drug, that has been excessively withdrawn from the market. It may be preferable to reintroduce benzbromarone in the market instead of using the new, costly drugs that carry a risk for unknown ADRs. Worldwide, the treatment of gout may be more successful with better (restricted) availability of benzbromarone [49-50].

Conclusion

This study showed that allopurinol 300 mg/day has a poor efficacy and tolerability profile when used to attain a biochemical predefined target level of sUr ≤0.30 mmol/l, following 2 months of treatment. In stage 2, benzbromarone 200 mg/day was more effective and better tolerated than probenecid 2,000 mg/day. Trial registration number: ISRCTN21473387.

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Chapter 3.3

Prevention of recurrent gouty arthritis with antihyperuricemic treatment: allopurinol, benzbromarone, and probenecid. A follow-up study

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Submitted

Abstract

Objectives

A lack of prospective long-term, high quality data exists that addresses the efficacy of antihyperuricemic treatment to prevent clinical symptoms, such as gouty arthritis. We conducted an observational follow-up study to assess the rate of recurrent gouty arthritis in patients receiving antihyperuricemic treatment after participating in a randomised controlled trial (RCT).

Methods

Eligibility criteria for the initial RCT were a diagnosis of gout, no history of allopurinol, benzbromarone or probenecid use, no relevant liver disease, a calculated creatinine clearance >50 ml/min, and an indication for starting antihyperuricemic therapy, defined as the presence of tophi or frequent gouty attacks (≥2/year).

After completion of the trial period primary aiming at biochemical correction, the rheumatologist was free to adjust the urate lowering treatment according to patient preferences. Patients who completed the RCT, and suffered from ≥2 attacks/year at baseline, were included in this prospective follow-up study with cross-sectional analysis. Each six months, the patient visited the rheumatologist again, the serum urate concentration was measured, and the patient was asked for the number of gouty attacks in the last period. Patients who continued using colchicine or NSAIDs on a daily basis, were included in a subgroup for evaluation of potential bias effects. Primary endpoint was the relative reduction in the rate of recurrent gouty attacks before start of urate lowering treatment and during the follow-up period of the trial.

Results

Ninety-six patients were enrolled in the initial RCT, and 50 patients were enrolled in the follow-up study; three patients were lost to follow-up. Twenty-four (48%) patients used allopurinol, 22 (44%) used benzbromarone, and 4 (8%) used probenecid. Furthermore, six patients did not stop colchicine or NSAID after the RCT, and were further analysed in a subgroup. Average duration of follow-up was 10.6 months. The incidence of gout attacks was largely reduced during follow-up compared to baseline rates: 74% of patients were free of gouty attacks (100% reduction), and 17% of patients had 50-99% reduction of gout attacks. Serum urate concentrations were 0.28 [± 0.08] mmol/l (mean [± standard deviation]).

Discussion

A high reduction in incidence of gout attacks was found. Results are better than obtained in most previous studies. This might be explained by the strict control of serum urate, and possibly by a selection bias of gout patients with good adherence. No correlation was found between reduction of gout attacks and sUr or study drug used, due to lack of power.

Conclusion

This follow-up study demonstrates that antihyperuricemic therapy is highly effective in the reduction and prevention of gout flares in gout patients under strict control of serum urate.

Introduction

Antihyperuricemic treatment in gout is indicated for patients suffering from recurrent gouty arthritis or tophaceous gout [1-2]. A lack of long-term, good-quality, prospective data exists addressing the efficacy of serum urate (sUr) lowering treatment to prevent clinical symptoms as gouty arthritis, Table 1 [3]. A number of studies shows that allopurinol (and other antihyperuricemic drugs like benzbromarone) does reduce serum urate, at least in the short term, and a well-documented relationship exists between serum urate and the incidence of acute gout [3, 11-12].

Table 1. Overview of trials that assessed reduction of gouty arthritis by currently available antihyperuricemic therapy with follow-up ≥6 months [3]

Ref.	Study drug and dosage	Comparator(s) and dosage	Trial design	No. of patients	Follow-up (m)	sUr decrease (%)	Patients free of gout attacks (%)	Decrease of gout attacks (%) [a]
[4-5]	Allopurinol 300-600 mg/day	Probenecid 1-2 g/day, or Sulphinpyrazone 400 mg/day	CT	21 vs. 19	10-24	38% vs. 39% (NS)	45% vs. 47% (NS)	-
[6]	Azapropazone 600 mg/day	Allopurinol 300 mg/day	CT	46 vs. 47	7.5	26% vs. 28% (NS)	74% vs. 55% (p=0.03)	-
[7]	Benzbromarone 40-80 mg/day	Baseline	CT	408	9.7	34% vs. 0% (p <0.001)	- [c]	37% (p <0.001)
[8]	Benzbromarone 50-100 mg/day	Baseline	CT [b]	6	12	25% vs. 0% (p <0.001)	- [c]	46% (p=0.01)
[9]	Benzbromarone 100-200 mg/day	Allopurinol 100-300 mg/day	RCT [b]	17 vs. 19	9-24	56% vs. 33% (p <0.001)	- [c] (NS)	88-100% (p<0.001)
[10]	Febuxostat 80-120 mg/day	Allopurinol 300 mg/day	RCT	255-250 vs. 251	12	45-52% vs. 33% (p<0.001)	30-36% vs. 36% (NS)	-

Legend: CT = controlled trial, m = months; no. = number; RCT = randomised controlled trial; ref. = reference; sUr = serum urate concentration

[a] Versus baseline; [b] Patients with renal function impairment; [b] No data available

In one randomised controlled trial (RCT) of allopurinol versus febuxostat, a high percentage of patients suffered from recurrent gouty arthritis in all three treatment groups (64-70%) during week 9-48, despite sUr concentrations that were considered adequate (in the febuxostat 80 and 120 mg groups) [10]. In another RCT, follow-up data of 25 patients with renal function impairment showed that 20% suffered from gouty bouts during 6-12 months, 4% during 12-18 months, and 0% during 18-24 months after urate-lowering therapy with allopurinol or benzbromarone was started (colchicine was stopped at 6 months of urate-lowering therapy) [9]. These data, and

extensive clinical experience, suggest that sUr lowering treatment is effective and cost-effective in preventing recurrent gout [13].
We conducted an observational follow-up study to assess the rate of recurrent gouty arthritis in patients receiving urate-lowering treatment after participating in a RCT [14].

Methods

Study design and inclusion criteria

Patients recently diagnosed with gout by a rheumatologist were asked to participate in a two-stage randomised controlled trial [10]. Eligibility criteria were: (1) a diagnosis of gout confirmed by microscopic evidence of urate crystals or otherwise complying with the American Rheumatology Association (ARA) criteria, (2) no history of use of one of the study drugs, (3) no history of liver disease, (4) no relevant renal disease defined as calculated creatinine clearance (cCrCl) ≥50 ml/min calculated by the formula of Cockcroft and Gault, and (5) an indication for sUr lowering therapy: presence of tophi or frequent attacks (≥2/year).
In stage 1, patients were given allopurinol 300 mg daily. When allopurinol was not tolerated or when the treatment goal of sUr ≤0.30 mmol/l was not reached after 2 months, patients directly switched to stage 2 treatment: benzbromarone 200 mg once daily (Desuric®; OTL Pharma, Breda, The Netherlands) or probenecid 1,000 mg (Probenecid Weimer®; Biokanol Pharma, Rastatt, Germany) twice daily. Prophylaxis of gouty episodes with colchicine 0.5-1 mg/day was prescribed until target sUr level was reached (sUr ≤0.30 mmol/l); when colchicine was not tolerated, a non-steroidal anti-inflammatory drug could be prescribed as an alternative. Each treatment regimen was evaluated after a treatment period of 2 months by measuring sCr, sUr, uCr and uUr.
After completion of the trial period, the rheumatologist was free to adjust the urate lowering agent or dose; a sUr target level of 0.30 mmol/l was used. Patients who suffered >2 attacks/ year before antihyperuricemic treatment, were included in the follow-up study. Each 6 months, the patients visited the rheumatologist again, serum urate concentrations were measured and patients were asked for the number of gouty attacks they experienced in the last year. A cross-sectional analysis was performed, and patients with an evaluation after ≥6 months follow-up were eligible. Patients who still used colchicine or NSAIDs on a daily basis, were included in a subgroup for evaluation of potential bias effects.
Primary endpoint of this follow-up study was the relative reduction of the rate of recurrent gouty arthritis before start of urate lowering treatment and during the follow-up period of the trial.
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

Ninety-six patients were enrolled in the randomised controlled trial. Nine patients were excluded from the follow-up study because of protocol violation (3) and poor adherence in stage 1 (allopurinol 300 mg/day) based on measured plasma oxipurinol levels <1.0 mg/l (6). Also, nine patients were lost to follow-up in stage 1 (5) and stage 2 (4) of the RCT. Furthermore, 22 patients did not suffer from 2 gouty attacks per year prior to start of urate lowering treatment and 6 patients were not willing to continue any urate lowering treatment after the initial trial period (predominantly because of intolerance). Thus, 50 patients were enrolled in the follow-up study (Table 2).

Table 2. Demographic and clinical characteristics at baseline

Characteristics (n=50)		
Age (y)	mean [± SD] range	58 [± 12] 41-86
Male gender		88%
Recurrent flares	2-4/y 5-9/y ≥10/y	48% 30% 22%
Body mass index (kg/m^2)	mean [± SD] range	28.8 [± 3.4] 22.5-36.3
Creatinine clearance	50-80 ml/min >80 ml/min	30% 70%
Centre	Leeuwarden Enschede	48% 52%
sUr (mmol/l)	mean [± SD] range	0.54 [± 0.07] 0.39-0.75
uUr (mmol/day)	mean [± SD] range	3.3 [± 1.2] 1.3-6.3
UrCl (ml/min per 1.73 m^2)	mean [± SD] range	3.5 [± 1.3] 1.5-7.6
Excretor-type [1]	underexcretor normal excretor overproducer	81% 13% 6%

Legend: SD = standard deviation; sUr = serum urate; uUr = urate excreted in urine; UrCl = urate clearance; y = year(s).

[1] Definitons of excretor-type: underexcretor UrCl <6.0 ml/min per 1.73 m^2; overproducer uUr >6.0 mmol/day; normal excretor UrCl ≥6.0 ml/min per 1.73 m^2 and uUr ≤6.0 mmol/day.

Table 3. Results of antihyperuricemic treatment after one year of follow-up.

Characteristics of antihyperuricemic treatment		
Allopurinol dosage (mg/day)	n mean [± SD] range	21 362 [± 91] 200-600
Benzbromarone dosage (mg/day)	n mean [± SD] range	18 147 [± 50] 100-200
Probenecid dosage (mg/day)	n mean [± SD] range	4 1,750 [± 500] 1,000-2,000
Follow-up duration (months)	n mean [± SD] range	 10.4 [± 3.8] 4.8-19.7
Outcome		
Frequency of gout attacks	0/year 0-1/year 1-2/year 2-4/year	79% 5% 9% 7%
Reduction of gout attacks (%)	100% 75-99% 50-74% other	79% 7% 5% 5%
sUr (mmol/l)	mean [± SD] range	0.28 [± 0.08] 0.15-0.55
sUr decrease (%)	mean [± SD] range	46 [± 17] % 12-71

Legend: SD = standard deviation; sUr = serum urate.

Three patients did not have an evaluation after ≥6 months (lost to follow-up). Six patients were not willing to stop colchicine or NSAIDs on a daily basis, and were further analysed in a subgroup. Results of remaining 47 patients are presented in Table 3. Average duration of follow-up was 10.6 months. Twenty-four (51%) patients used allopurinol, 19 (40%) benz-bromarone, and 4 (9%) probenecid. Incidence of gout attacks was largely reduced during follow-up compared to baseline rates: 75% of patients were free of gouty attacks (100% reduction), and 17% of patients had 50-99% reduction of gout attacks. The results in the

subgroup of patients who continued colchicine or NSAID revealed that inclusion of this subgroup did not significantly affect the overall outcome results (Table 3).
Serum urate concentrations were 0.28 [± 0.08] mmol/l (mean [± standard deviation]). We did not find a significant relationship between the incidence of gout attacks and serum urate concentration reached, or study drug used.

Discussion

This follow-up study demonstrates that antihyperuricemic drug therapy is highly effective in reducing and preventing gout attacks in gout patients with normal renal function. Results are better than obtained in most previous studies (Table 1). This might be explained by the strict control of serum urate in this study (mean 0.28 mmol/l), and possibly by a selection bias of patients with good adherence. In a retrospective study, it was found that lower sUr were significantly associated with better control of gout attacks [11]. Also, Pérez-Ruiz *et al.* found good control of gout attacks with a strict control of serum urate [9].
In our study, no correlation was found between the incidence of gout attacks and serum urate concentration reached, or study drug used. This is caused by lack of power: only nine patients with gout attacks were recorded.
A matter of debate to which target sUr should be used, still exists [15]. The European recommendations use 0.36 mmol/l in general, while the British guideline uses 0.30 mmol/l [2, 16]. It is important to consider that 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 [17]. Solubility of urate is 0.41 mmol/l at 37 °C in presence of sodium concentration of 140 mmol/l, 0.36 mmol/l at 35 °C, and 0.27 mmol/l at 30 °C [18]. Since body temperature is the lowest in the extremities, gout symptoms usually occur in these parts. Therefore, as well as from clinical data, target sUr levels should be below 0.42 mmol/l at least, a value often mentioned in the literature from theoretically reasons, and preferably below 0.30 mmol/l, as advised in the British guideline [2].

Conclusion

This follow-up study demonstrates that antihyperuricemic therapy with allopurinol, benzbromarone or probenecid, is highly effective in reducing and preventing gout attacks in gout patients with a calculated creatinine clearance >50 ml/min, under strict control of serum urate.

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Chapter 3.4

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

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Abstract

Objectives

To compare the efficacy and tolerability of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day to attain a target sUr ≤0.30 mmol/l (5 mg/dl).

Methods

A randomised, controlled, open-label, multi-centre trial was conducted in gout patients with renal function defined as cCrCl ≥50 ml/min. Patients were treated with 300 mg allopurinol or 100 mg benzbromarone once daily (stage 1). When sUr ≤0.30 mmol/l was not attained after 2 months, dosage was doubled to allopurinol 300 mg twice daily or benzbromarone 200 mg once daily (stage 2). Primary endpoint was treatment success in either of both stages, defined as clinical tolerability and attainment of biochemical target serum urate concentration.

Results

Sixty-five patients were enrolled in stage 1, 36 patients received allopurinol and 29 received benzbromarone. Fifty-five patients (85%) were evaluated for analysis of stage 1. At stage 1, the success rates are 8/31=0.26 (26%) and 13/25=0.52 (52%), and difference is -0.26 (CI 95% from -0.486 to -0.005), p=0.049. At stage 2, the success rates are 21/27=0.78 (78%) and 18/23=0.78 (78%), and difference is -0.005, (CI 95% from -0.223 to 0.220), p=1.00. Two patients stopped allopurinol and 3 patients stopped benzbromarone because of adverse drug reactions (ADR).

Conclusion

Increase of allopurinol dosage from 300 to 600 mg/day and benzbromarone dosage from 100 to 200 mg/day according to target sUr, gives significantly higher success rates (both 78% success in sUr ≤0.30 mmol/l). No significant differences in treatment success between benzbromarone and allopurinol groups were found after dosage escalation (controlled-trials.com number ISRCTN49563848).

Introduction

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 of serum urate (0.30 mmol/l versus 0.36 mmol/l) [2]. In order to reach the target serum urate (sUr) concentration, the EULAR recommendations advise to titrate allopurinol dosage up to a maximum of 900 mg/day. However, historically a fixed dosage of 300 mg/day is mostly used in clinical research and clinical practice [3]. Data on clinical efficacy and tolerability of antihyperuricemic treatment are scarce, especially on higher than standard dosages [4]. In one study, allopurinol 600 mg/day was given to 19 patients, resulting in a sUr decrease of 44% [± 13%] (mean ± standard deviation) compared with baseline, and in 52% success in attaining sUr ≤0.30 mmol/l (5.0 mg/dl) [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 using allopurinol 600 mg/day [6]. In a randomised controlled trial of benzbromarone 200 mg/day versus probenecid 2,000 mg/day (ISRCTN 21473387, www.controlled-trials.com), we found a decrease of sUr of 64% [± 9%] compared to baseline, and in 92% success in attaining sUr ≤0.30 mmol/l [7].

The goal of antihyperuricemic treatment is to reduce the serum urate (sUr) level below the threshold of supersaturation to prevent any gouty attack by allowing the dissolution of existing monosodium urate (MSUr) crystals in the joints and to stop the deposition of new crystals [1-2]. 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 level attained, and on mechanical stress as attacks might be predisposed to joints affected by osteoarthritis [9-13].

According to the EULAR 2006 recommendations, treatment goal of antihyperuricemic drug therapy is to reach target sUr levels below 0.36 mmol/l (6.1 mg/dl) [1]. Historically, the target serum urate level 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 the lowest and the solubility of monosodium urate is smaller. It is shown that recurrent gouty attacks are better prevented and that tophi dissolve more quickly with target serum urate levels below 0.30 mmol/l (5.0 mg/dl) compared with levels 0.30-0.36 mmol/l [15-19]. For this reason, the British Guideline 2007 sets the sUr treatment goal for gout patients at ≤0.30 mmol/l [2].

In order to get 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.

Methods

This prospective, multi-centre, open label, randomised controlled trial was carried out in successive patients, previously untreated, recently diagnosed with gout 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 presence of tophi, (2) no history of having used one of the study drugs, (3) no relevant liver disease, (4) renal function defined as calculated creatinine clearance (cCrCl) ≥50 ml/min calculated by the formula of Cockcroft and Gault, and (5) an indication for antihyperuricemic drug therapy: presence of tophi or frequent attacks (>2/year) [20-24]. Before entering the study and after each treatment period, liver function, serum creatinine (sCr) and calculated Cr clearance, sUr, urinary creatinine excretion (uCr), and urinary urate excretion (uUr) on unrestricted purine diet were measured. In addition, in patients using allopurinol, serum oxipurinol concentrations were measured after each treatment period. Underexcretion of urate was defined as urate clearance (UrCl) <6.0 ml/min per 1.73 m^2 [24]. Urate clearance was calculated by urinary volume (converted to ml/min)*urinary urate concentration/sUr and normalised for a body surface area of 1.73 m^2. Overproduction of urate was defined as uUr >6.0 mmol/day. Normal excretion of urate was defined as UrCl ≥6.0 ml/min per 1.73 m^2 and uUr ≤6.0 mmol/day. Reported adverse events were checked on causality by the Naranjo Causality Scale [25]. Reported adverse events classified as doubtful were not included as adverse drug reactions in the tolerability evaluation.

When included in the study, patients were assigned to an inclusion number by the rheumatologist (blinded) and consequently 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 was from July 2006 until December 2007.

Patients were given allopurinol 300 mg once daily (several generic brands) in a step-up dosage scheme (100-200-300 mg/day, dosage raised every week) or benzbromarone 100 mg once daily (Desuric®; Prostrakan, Galashiels, United Kingdom). When treatment was tolerated and the treatment goal of sUr ≤0.30 mmol/l was not reached after 2 months, allopurinol dosage was doubled at once to 300 mg twice daily and benzbromarone dosage to 200 mg once daily. The dosage interval of allopurinol was set at twice daily at the higher dosage, because gastro-intestinal tolerability might be better. Also, from a pharmacodynamic point of view, twice daily dosage yields higher serum trough concentrations which might give better enzyme inhibition. Treatment was evaluated again after 2 months. When treatment was not tolerated and patient withdrew from treatment, this was categorised as failure. When treatment was tolerated and target sUr was reached patient was categorised as successful. 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 target sUr level was reached (sUr ≤0.30 mmol/l); when colchicine was not tolerated, a non-steroidal anti-inflammatory drug could be prescribed as an alternative.

Primary endpoint was the percentage of patients tolerating the antihyperuricemic medication and attaining sUr concentration below 0.30 mmol/l after stage 1 or stage 2. Secondary endpoint was the relative decrease of sUr concentration attained with each treatment regimen.
The study was approved by the Medical Ethical Review Board of the participating hospitals, and written informed consent was obtained from all participating patients.

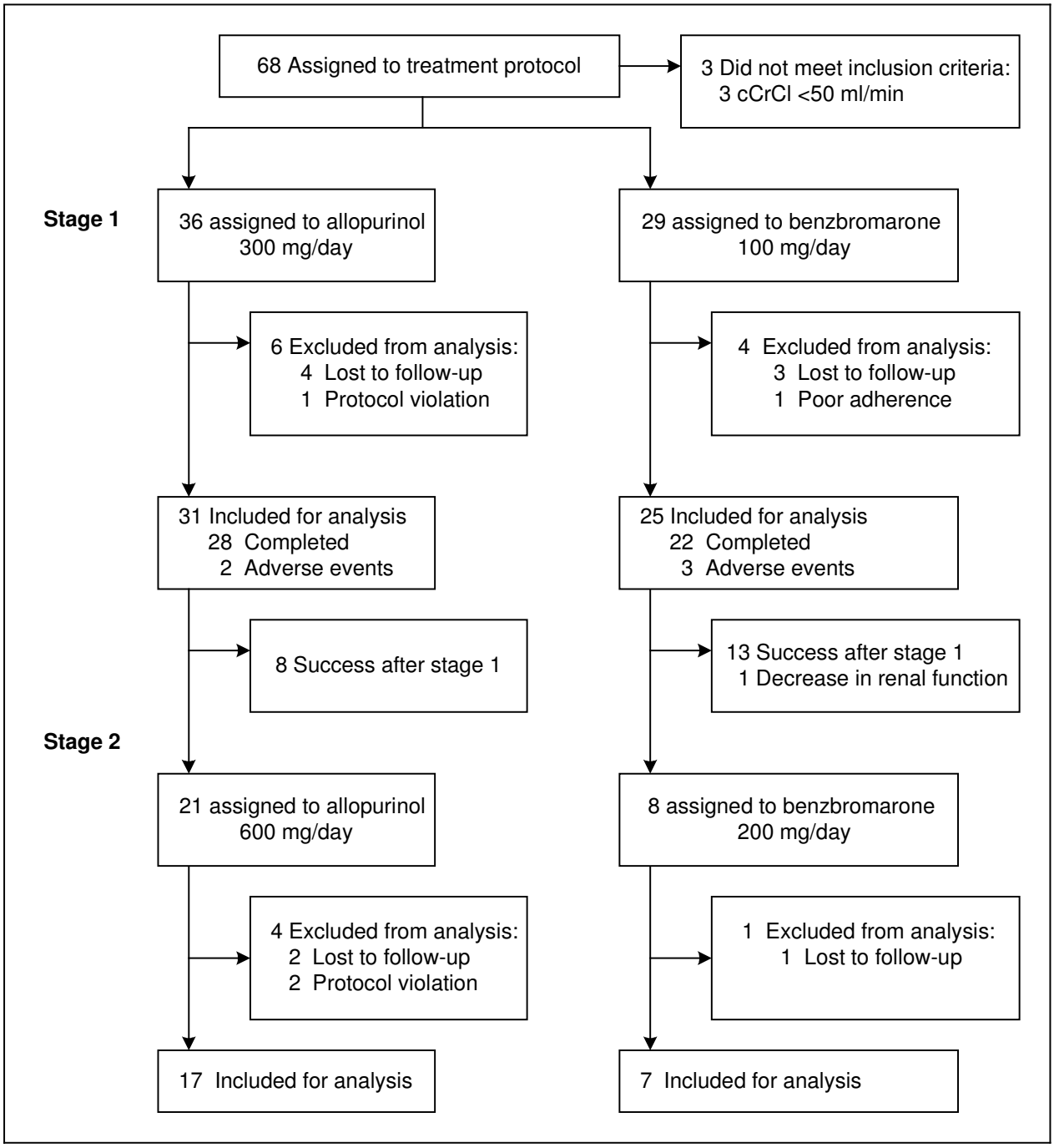
Statistics

Power calculation was performed indicating 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, α=0.05, β=0.20) [5-7]. We expected a loss to follow-up of 25%, rendering a minimum of 60 patients for the study. SPSS 15.0 and 16.0 for Windows (SPSS Inc., Chicago, IL, USA) were used for data collection, data validation, data selection, and statistical analysis. Student's two-sided t-test and Fischer-Boschloo's unconditional test were used to compare the effectiveness of allopurinol and benzbromarone; 95%-confidence intervals of proportions were calculated using binomial distribution, and 95%-confidence intervals of differences of proportions using Agresti-Caffo [26-27]. Normality was verified with Kolmogorov-Smirnov analysis. A p-value <0.05 was considered statistically significant.

Results

Sixty-eight patients were enrolled in the study (Figure 1). Violation of inclusion protocol occurred in three patients (calculated creatinine clearance 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 fifty patients (77%) for analysis of stage 1+2.
Results of stage 1 and 2 are presented in Table 2 and Figure 2. Treatment target was reached in 8 out of 30 patients (26%) applying allopurinol 300 mg/day; after increase of dosage, overall treatment success with allopurinol 300-600 mg/day was 21 out of 27 patients (78%). With benzbromarone 100 mg/day, treatment target was reached in 13 out of 25 patients (52%); after increase of dosage, overall treatment target with benzbromarone 100-200 mg/day was reached in 18 out of 23 patients (78%). Two patients stopped allopurinol and 3 patients stopped benzbromarone because of adverse drug reactions (ADR), Table 3. No additional ADR were reported after increase of dosages of allopurinol and benzbromarone. At stage 1, the success rates are 8/31=0.26 and 13/25=0.52, and the difference is 0.26-0.52= -0.26 ($CI_{95\%}$ from -0.486 to -0.005), p=0.049. At stage 2, the success rates are 21/27=0.78 and 18/23=0.78, and the difference is -0.005, ($CI_{95\%}$ from -0.223 to 0.220), p=1.00.

Figure 1. Flow of participants through each stage of the study.



Legend: cCrCl: calculated creatinine clearance.

Table 1. Demographic and clinical characteristics [1]

Characteristics		Allopurinol (n=36)	Benzbromarone (n=29)
Demographics			
Age (y)	mean [± SD] range	58.6 [± 12.3] 33-77	59.6 [± 11.3] 39-80
Male gender	(%)	81%	83%
Tophaceous gout	(%)	53%	48%
Recurrent flares	0-2/y 3-5/y >5/y	18% 59% 22%	17% 50% 33%
Body mass index (kg/m^2)	mean [± SD] range	29.4 [± 4.8] 21.5-42.6	30.5 [± 6.9] 17.2-54.9
Calculated creatinine clearance	30-50 ml/min 50-80 ml/min >80 ml/min	(3 excluded) 22% 78%	(0 excluded) 39% 61%
Research site	Medisch Centrum Leeuwarden Ziekenhuisgroep Twente Medisch Spectrum Twente	28% 41% 31%	24% 45% 31%
Urate characteristics			
sUr (mmol/l)	mean [± SD] range	0.54 [± 0.09] 0.39-0.83	0.51 [± 0.08] 0.34-0.70
uUr (mmol/day)	mean [± SD] range	3.4 [± 1.3] 1.5-7.7	3.4 [± 1.3] 1.3-6.3
UrCl (ml/min/1.73m^2)	mean [± SD] range	3.7 [± 1.3] 1.5-6.8	3.9 [± 1.3] 1.6-6.4
Excretor-type	underexcretor normal excretor overproducer	94% 3% 3%	89% 3% 8%

Legend: NS = non-significant (p>0.05); sUr = serum urate; uUr = urate excreted in urine; UrCl = urate clearance; y = year(s).

[1] Data shown as mean [± standard deviation] or percentage, unless stated otherwise.

Reduction of serum urate levels with allopurinol were 33% [± 13%] using 300 mg/day, and 49% [± 14%] using 600 mg/day, compared to baseline sUr. Increase of allopurinol dosage to 600 mg/day in patients above target sUr after stage 1, resulted in an additional sUr decrease of 32% [± 16%] compared to the sUr attained in these patients using allopurinol 300 mg/day. Using benzbromarone, reduction of serum urate levels: 42% [± 15%] using 100 mg/day, and 46% [± 8%] using 200 mg/day, compared to baseline sUr. Increase of benzbromarone dosage to 200 mg/day in patients above target sUr after stage 1, resulted in an additional sUr decrease of 29% [± 6%] compared to the sUr attained in these patients using benzbromarone 100 mg/day.

Table 2. Efficacy of allopurinol 300-600 mg/day versus benzbromarone 100-200 mg/day after stage 1 and stage 2 [1]

		Allopurinol	Benzbromarone	p-value
Stage 1 and 2 results		**(n=27)**	**(n=23)**	
Dosage (mg/day)		300-600	100-200	
Treatment goal reached	sUr ≤0.30 mmol/l $CI_{95\%}$	21 (78%) 59-89%	18 (78%) 58-90%	1.00
Treatment goal not reached	withdrawn due to ADR sUr 0.31-0.36 mmol/l sUr >0.36 mmol/l	2 (7%) 2 (7%) 2 (7%)	3 (13%) 2 (9%) 0 (0%)	0.62 1.00 0.34
Stage 1 results		**(n=31)**	**(n=25)**	
Dosage (mg/day)		300	100	
Duration (months)	mean [± SD] range	2.3 [± 0.8] 1.5-4.9	2.2 [± 0.7] 1.6-3.2	0.93
Treatment goal reached	sUr ≤0.30 mmol/l $CI_{95\%}$	8 (26%) 12-45%	13 (52%) 33-70%	0.049
Treatment goal not reached	withdrawn due to ADR sUr 0.31-0.36 mmol/l sUr >0.36 mmol/l	2 (7%) 12 (39%) 8 (27%)	3 (12%) 2 (8%) 7 (28%)	0.62 0.01 1.00
sUr reached (mmol/l)	mean [± SD] range	0.34 [± 0.08] 0.21-0.49	0.29 [± 0.08] 0.16-0.45	-
ΔsUr from baseline		-33% [± 13%]	-42% [± 15%]	0.04
uUr (mmol/day)	mean [± SD] range	2.2 [± 1.2] 0.5-6.1	4.4 [± 1.7] 1.5-8.4	<0.001

(Table 2 continued)

		Allopurinol	Benzbromarone	p-value
UrCl (ml/min per 1.73 m^2)	mean [± SD] range	3.6 [± 1.5] 1.0-8.0	4.9 [± 2.2] 3.0-20.6	<0.001
Serum oxipurinol (mg/l)	mean [± SD] range	13.1 [± 10.4] 3.9-51.3	-	-
Stage 2 results [2]		**(n=17)**	**(n=7)**	
Dosage (mg/day)		600	200	
Duration (months)	mean [± SD] range	2.5 [± 0.7] 1.5-4.9	2.3 [± 0.8] 1.6-3.2	0.71
sUr reached (mmol/l)	mean [± SD] range	0.27 [± 0.07] 0.18-0.38	0.28 [± 0.04] 0.23-0.35	-
Decrease of sUr	from baseline from stage 1	-49% [± 14%] -32% [± 16%]	-46% [± 8%] -29% [± 6%]	-
uUr (mmol/day)	mean [± SD] range	2.1 [± 1.0] 1.1-3.5	4.9 [± 2.2] 2.1-8.1	-
UrCl (ml/min per 1.73 m^2)	mean [± SD] range	4.3 [± 1.5] 2.0-6.6	10.3 [± 3.7] 4.6-15.3	-
Serum oxipurinol (mg/l)	mean [± SD] range	17.0 [± 9.9] 4.9-41.7	-	-

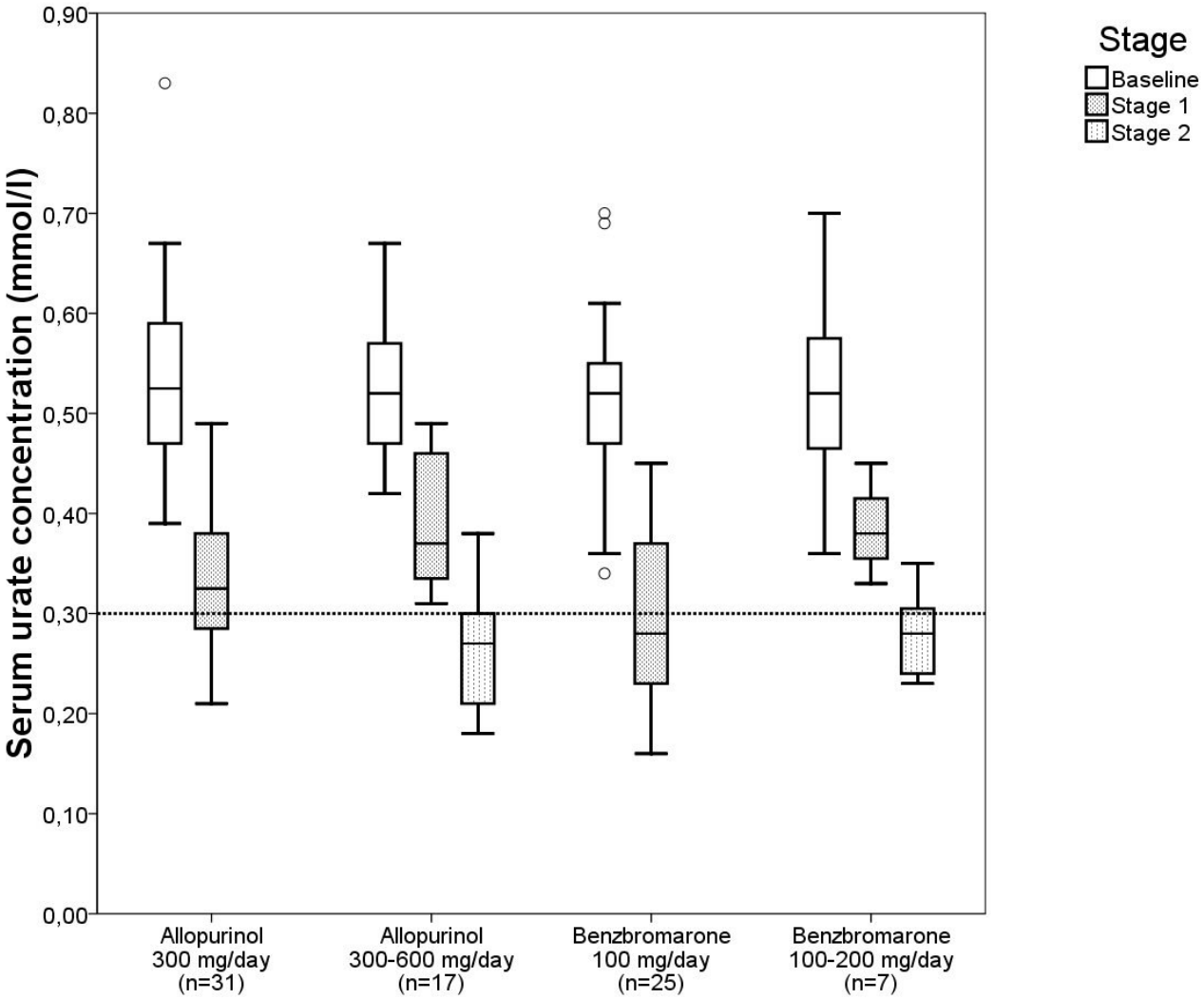
Legend: $CI_{95\%}$ = 95% confidence interval; NS = non-significant (p>0.05); sUr = serum urate; uUr = urate excreted in urine; UrCl = urate clearance. ADR = adverse drug reaction

[1] Data shown as n(%) or mean [± standard deviation] and range, unless stated otherwise.

[2] No statistical comparisons were done for stage 2 results because of incomparable groups due to selection bias

Figure 2. Box-plot diagram for serum urate concentrations at baseline, and after stage 1 and stage 2 treatment with allopurinol or benzbromarone

Results are depicted in 2 groups for each drug: all patients who completed stage 1 treatment, and all patients who completed stage 1 and 2, respectively.



Legend: o = outlying value; dotted line = target serum urate concentration

Table 3. Results of reported adverse drug reactions (ADRs) leading to withdrawal, and all reported ADRs [1]

Adverse drug reaction (ADR)	Allopurinol (n=30)	Benzbromarone (n=25)
Number of patients with ADR	2 (7%) / 2 (7%)	3(12%) / 5 (20%)
$CI_{95\%}$	1-22% / 1-22%	3-31% / 7-40%
Type of ADR		
Dizziness and flushing	- / -	1 (4%) / 1 (4%)
Gastro-intestinal	- / -	2 (8%) / 2 (8%)
Hepatitis [2]	- / -	- / -
Gout flares	- / -	- / 1 (4%)
INR increase	- / -	- / 1 (4%)
Rash / skin reactions	2 (7%) / 2 (7%)	- / -
severe skin reactions	- / -	- / -

Legend: $CI_{95\%}$ = 95% confidence interval;

[1] Adverse drug reactions expressed as ADR leading to withdrawal (n(%)) / total ADR (n(%)) reported; one patient could report more than one ADR.

[2] Grade 2, 3 or 4 liver enzyme elevations.

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 dosage to 600 mg/day ($p<0.001$). Benzbromarone gives significant better treatment success at the starting dose (stage 1) compared to allopurinol, as was demonstrated in previous trials as well [28-29]. After dosage escalation (stage 2), no significant difference was found anymore in treatment success of allopurinol versus benzbromarone.

We found a treatment success rate of allopurinol 300-600 mg/day (78%), which was higher than was reported in previous studies. Rundles *et al.* found a treatment success rate of 53% ($CI_{95\%}$ 29-76%) in 19 patients using allopurinol 600 mg [5]. Baseline sUr values in these 19 patients (sUr 0.56 [± 0.11] mmol/l) were comparable with values in our study. We might have obtained better results by using a twice-daily dosage scheme whereas Rundles *et al.* used once daily, as higher trough oxipurinol concentrations might give better xanthine oxidase inhibition. Allopurinol is approved for use up to 900 mg/day [2]. Even better results might be possible using this maximum dosage. In the Netherlands, a national guideline recommends a maximum of 700 mg allopurinol per day [30].

Treatment duration of 2 months might be considered too short for treatment evaluation, especially in patients with poor renal urate excretion and consequently longer serum urate half-lives. In non-gout subjects serum urate half-life is about 0.85 days [31]. In gout patients with severe underexcretion of urate of UrCl 1.5 ml/min (reference value is about 6 ml/min per 1.73 m^2), thus we estimated that corresponding serum urate half-life is about 4 days. As steady-state is established within 5 half-lifes, a 2-months treatment period should be sufficient for evaluation of allopurinol treatment, even when we take the allopurinol step-up dosage scheme into account. In addition, decrease of sUr with allopurinol 300 mg/day in our study is comparable with previous studies with a longer treatment period [32].

Treatment success of benzbromarone increased from 52% to 78% by titrating dosage up to 200 mg/day (p=0.075). Treatment success of benzbromarone was somewhat lower than expected from our previous study, in which we found a 92% treatment success with benzbromarone 200 mg/day in 24 patients [7]. A lower success percentage in the current study might be caused by some non-adherent patients, due to a different trial design (i.e. exclusion of patients with low medication adherence to allopurinol in subsequent benzbromarone or probenecid treatment group), and lower tolerability rate. We did not find other data on the sUr lowering effect and treatment success of benzbromarone 200 mg/day.

Adherence to gout medication is 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 oxipurinol concentrations increased in each individual in 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.

In this study, all patients were referred to a rheumatologist, which might predispose to inclusion of patients with more severe gout. Better results might be obtained in patients with less severe gout having lower baseline sUr levels.

Allopurinol of different (generic) brands was used, which might enhance the variance of results. In the Netherlands, the requirement for bio-equivalence is that the 90%-confidence interval must be within 80-125% of the reference value.

A matter of debate to which target sUr should be aimed for, still exists [35]. In the recent EULAR recommendations, a less strict target sUr of ≤0.36 mmol/l is proposed for gout treatment in general, whereas in case of severe gout the treatment target might be set lower.[1] Using a treatment goal of sUr of ≤0.36 mmol/l, treatment successes would be 85% for allopurinol and 87% for benzbromarone.

Tolerability rates found for allopurinol and benzbromarone did not statistically differ from data in other studies. All adverse drug reactions reported for allopurinol and benzbromarone occurred in stage 1, and these reactions have been described before [5, 36-37]. Gout flares might be caused by starting antihyperuricemic drug therapy due to mobilisation of urate related to rapid decline of sUr. One patient developed generalised exanthema after allopurinol was started at

100 mg/day, and one patient developed exfoliative dermatitis during stage 1. No hepatitis, defined as grade 2, 3 or 4 liver enzyme elevations, was seen with allopurinol or benzbromarone during the study period. Severe hepatotoxicity of benzbromarone is seen in rare cases, and led to withdrawal of benzbromarone in many countries. Recently, a mechanism for this hepatotoxicity was reported [38]. Patients with high renal urate clearances, e.g. by using uricosurics, have an increased risk of urate nephrolithiasis. Therefore, benzbromarone is relatively contra-indicated in patients with normal renal urate clearances. In our group of patients receiving benzbromarone, no urate nephropathy, nephro- or urolithiasis was reported, and no nephropathy was found by calculating creatinine clearances before and after therapy.

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) allopurinol dosage then should be adjusted to renal function, and (2) the efficacy of benzbromarone drops gradually with decreasing renal function to inefficacy in presence of cCrCl lower than about 25 ml/min.

We used sUr as a surrogate parameter for clinical success. Previous studies found that attained sUr is inversely related to prevention of recurring gout flares and to velocity of size reduction of tophi [16-19]. Therefore, sUr is considered an important parameter in clinical practice to evaluate success of antihyperuricemic drug therapy for gout in the long-term.

There are few therapeutic options available to lower sUr to target levels other than the drugs used in this study. The uricosuric drug sulfinpyrazone is not widely used due to its adverse effects profile [39]. Probenecid was found to be less effective and less tolerated than benzbromarone [7]. Febuxostat, a novel xanthine oxidase inhibitor, was found to be more effective than allopurinol [32], however allopurinol dosage 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 dosage (i.e. 600 mg/day) in the aforementioned comparative study might have given endpoint results in which allopurinol and febuxostat would be quite similar.

Another antihyperuricemic drug under development is pegylated uricase, aimed for patients unresponsive to current antihyperuricemic treatments. Since combination therapy of allopurinol and a uricosuric (benzbromarone or probenecid) gives additional lowering of serum urate, this might also be a beneficial option [41]. The impact of gout on work absence and productivity is substantial, so pharmaco-economic studies between the newer and older (out of patent) drugs, like allopurinol and benzbromarone, are necessary [42].

Conclusion

In patients with gout and renal function defined as cCrCl ≥50 ml/min, increasing allopurinol dosage up to 600 mg/day and benzbromarone dosage up to 200 mg/day gives better treatment successes (both 78% success regarding sUr ≤0.30 mmol/l). No significant differences in treatment success were found between allopurinol and benzbromarone after dosage increase, and this increased dosage was well tolerated for both drugs.

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