Concise report

Sex differences in response to allopurinol and benzbromarone in gout: a retrospective cohort study

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Abstract

Objective Owing to lower mean uric acid excretion in women compared with men, uricosuric agents might be preferred in women over xanthine oxidase (XO) inhibitors. We therefore investigated the differences in response to two urate-lowering therapies (ULTs) with different modes of action within and between sexes.

Methods This retrospective cohort study included patients with a clinical diagnosis of gout who started allopurinol and/or benzbromarone. The successful response to ULT, defined as reaching a serum uric acid (sUA) target of <0.36 mmol/l within 6 months after commencing ULT, was compared between allopurinol and benzbromarone in women and men. Effect modification by sex on differences in response was evaluated.

Results Allopurinol was started in 255 women and 1045 men, and benzbromarone in 60 women and 205 men. After 6 months, the proportions of women reaching the sUA target were 58.4% and 66.7% for allopurinol and benzbromarone, respectively (difference, −8%; 95% CI: −22%, 5%). The respective proportions in men were 61.0% and 75.6%, respectively (difference, −15%; 95% CI: −21%, −8%). Corrected for confounding, the odds ratio (OR) of reaching the target on benzbromarone *vs* allopurinol within women was 0.91 (95% CI: 0.47, 1.75), and within men 1.55 (95% CI: 1.04, 2.32). Corrected for confounding, sex was not an effect modifier of the difference in allopurinol and benzbromarone response (OR, 0.59; 95% CI: 0.28, 1.24).

Conclusion This study did not demonstrate between-sex differences regarding the response to either a uricosuric agent or an XO inhibitor, negating different treatment choices by sex.

Key words: gout, urate-lowering therapy, allopurinol, benzbromarone, women, men

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Key messages

- The clinical manifestations of gout are different between women and men.
- There are no between-sex differences regarding response to either benzbromarone or allopurinol.

Introduction

Gout is a preferential male disease, with a male-to-female prevalence ratio of 3–4:1 [1]. Given this distribution, less is known about gout in women, although the incidence of gout in women has doubled over the past two decades [2]. In recent years, the attention on gout in women has increased. Studies show

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that the clinical manifestation of gout is different between women and men. For example, gout occurs in women at an older age and is more frequently accompanied by co-morbidities, and women with gout use diuretics more frequently [3–5]. To our knowledge, there are few data on a possible difference in the response to urate-lowering therapy (ULT) between women and men. Medication studies mostly include men, and no separate data for women have been published, which precludes subgroup analyses [6, 7]. However, this is a subject of interest, because women and men differ on many levels, such as lifestyle and biological processes, which could influence the response to medication [8, 9].

An important difference is that women with gout seem to have a lower mean uric acid excretion in comparison to men with gout [10–12]. Also, in a large cohort of patients without gout, who suffered from renal stones, female patients showed significantly lower uric acid excretion compared with male patients [13]. This, possibly more common, renal underexcretion of uric acid in women with gout leads to two hypotheses regarding the response to ULT. Firstly, there might be a better response to a uricosuric agent (benzbromarone) compared with a xanthine oxidase (XO) inhibitor (allopurinol) in female patients. Secondly, a relatively better response to a uricosuric agent compared with an XO inhibitor might be expected in female gout patients compared with male gout patients.

Therefore, in this retrospective cohort study in secondary rheumatology care, we investigated the differences within and between sexes in the response to two ULTs with different modes of action.

Methods

Study design

A retrospective cohort study was conducted in two rheumatology clinics, the Sint Maartenskliniek Nijmegen and Rijnstate Hospital Arnhem, The Netherlands. Data on patient, disease and treatment characteristics were collected from electronic health records. Approval from the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, 2018-4692) was obtained. Patient informed consent was sought according to Dutch law and the local rules of each participating centre.

Participants

Patients, ≥18 years of age, with a clinical diagnosis of gout (according to 2015 ACR/EULAR gout classification criteria and/or clinical diagnosis by a rheumatologist [14]) who had a minimum follow-up of 6 months between January 2010 and September 2018, were ULT naive and started allopurinol and/or benzbromarone during follow-up were included in this cohort. ULT-naive patients were selected to create a clear starting point. Given that allopurinol is the first-choice medication in the participating

hospitals, patients who used benzbromarone were often switching from allopurinol or adding benzbromarone to allopurinol during follow-up. If a patient had a treatment period on both ULTs, both periods were included in the study. A treatment period was defined from the start of ULT until discontinuation or the end of follow-up (owing to either being lost to follow-up or the study end). Patients without any serum uric acid (sUA) measurements after initiation of ULT were excluded.

Outcome measures

At baseline (commencement of the ULT treatment period, either allopurinol or benzbromarone), patient and disease characteristics were assessed. To measure the difference in response, a successful response to ULT was defined as reaching an sUA target of <0.36 mmol/l [15] within 6 months after start of ULT. Secondary outcomes were the time to reach the sUA target at any time during follow-up after the start of ULT, and the ULT dose at the time of reaching the sUA target.

Statistical analyses

No formal sample size calculation was made because a convenient sample was used. All comparisons were made between sexes and between allopurinol and benzbromarone. Baseline differences were, depending on distribution, evaluated using Student's two-sample t test or the Mann–Whitney U test for continuous variables, and the χ^2 test or Fisher's exact test for categorical variables. The primary outcome for a successful response to ULT treatment was presented as a proportion, the difference in proportions and 95% CI, evaluated by the two-sample proportion z test. Using logistic regression, after univariate analysis of baseline characteristics, the multivariate model included correction for the confounders sUA baseline levels, baseline estimated glomerular filtration rate (eGFR) level and use of diuretics. Effect modification of sex on between-drug response differences was analysed using an interaction term, sex*ULT. Time to reach the target (any time during follow-up) was analysed by Cox proportional hazard modelling, with correction for sUA baseline levels. Here also, the interaction term for sex*ULT was tested for significance. Furthermore, the model included an interaction term for time*ULT to meet the proportional hazard assumption of stable hazard rate (HR) over time, with time being divided into the first 120 days after initiation of ULT and the period after 120 days, based on HR distribution over time. Finally, the ULT dose at the moment of reaching the target was evaluated by linear regression corrected for sUA baseline levels, baseline eGFR levels and age. All analyses were done using cluster variance analyses to account for interdependence between groups, because patients could be included in both the allopurinol and benzbromarone treatment groups. Analyses were conducted using STATA/IC v.13.1 (StataCorp, College Station, TX, USA) and using complete case analysis.

Results

Demographics

In this cohort, 1300 and 265 patient treatment periods were included in the allopurinol and benzbromarone group, respectively. Of the patients who started benzbromarone during follow-up, 251 patients did so in addition to allopurinol ($n = 91$) or switched from allopurinol ($n = 160$), whereas 14 patients were naive starters.

Clinical characteristics at time of start of ULT are described in Table 1. Women in both ULT treatment groups had a significantly older mean age, more co-morbidities, more frequent use of diuretics and higher baseline sUA, compared with men. Both women and men had a lower baseline level of sUA at the start of benzbromarone treatment compared with the baseline level before the start of allopurinol. Also, both women and men treated with benzbromarone had a lower eGFR compared with allopurinol users.

Successful response to ULT

Within 6 months after commencement of ULT, the proportions of women who had reached the target sUA were 58.4% and 66.7% for allopurinol and benzbromarone, respectively (difference, −8%; 95% CI: −22%, 5%). The proportions in men were 61.0% and 76.1% in allopurinol and benzbromarone users, respectively (difference, −15%; 95% CI: −22%, −9%). The corrected odds ratio (OR) of response to benzbromarone *vs* allopurinol within women was 0.91 (95% CI: 0.47, 1.75), and within men 1.61 (95% CI: 1.08, 2.41). The corrected OR of response to allopurinol in women compared with men was 1.38 (95% CI: 0.95, 2.02), and the OR for benzbromarone response for women compared with men was 0.79 (95% CI: 0.40, 1.58). Corrected for confounding, sex was not an effect modifier of the difference in allopurinol and benzbromarone response (OR 0.57; 95% CI: 0.27, 1.20).

TABLE 1 Baseline patient and disease characteristics

Characteristic	Allopurinol			Benzbromarone		
	Women (n = 255)	Men (n = 1045)	P-value[a]	Women (n = 60)	Men (n = 205)	P-value[a]
Age, years, median (IQR)	74.9 (67.3–81.6)	63.7 (54.4–72.4)	<0.001	75.8 (67.5–81.9)	66.3 (57.6–75.5)	<0.001
Current alcohol use, n (%)	88 (34.5)	696 (66.7)	<0.001	18 (30)	133 (64.9)	<0.001
Co-morbidities, n (%)						
Hypertension	176 (69.0)	496 (47.5)	<0.001	43 (71.7)	104 (50.7)	0.004
Renal impairment	95 (37.3)	195 (18.7)	<0.001	25 (41.7)	48 (23.4)	0.005
Diabetes mellitus	93 (36.5)	204 (19.5)	<0.001	24 (40)	45 (22.0)	0.009
Diuretics use, n (%)	169 (66.3)	403 (38.6)	<0.001	45 (75)	99 (48.3)	<0.001
Renal function, eGFR, ml/min/1.73 m², median (IQR)	46 (34–60)	70 (57–87)	<0.001	38.5 (31.5–50.5)	65.5 (46.5–82)	<0.001
History or presence of tophi, n (%)	97 (38.0)	276 (26.4)	<0.001	29 (48.3)	75 (36.6)	0.101
Erosive, n (%)	41 (16.1)	188 (18.0)	0.472	10 (16.7)	48 (23.4)	0.266
Crystal-proven gout, n (%)	190 (74.5)	734 (70.2)	0.177	46 (76.7)	144 (70.2)	0.331
Number of joints involved[b], %			0.448			0.477
Monoarthritis	42 (16.5)	202 (19.3)	–	9 (15)	37 (18.1)	–
Oligoarthritis	144 (56.5)	546 (52.3)	–	33 (55)	94 (45.9)	–
Polyarthritis	67 (26.3)	282 (27)	–	18 (30)	73 (35.6)	–
Baseline serum uric acid, mmol/l, mean (S.D.)	0.56 (0.12)	0.52 (0.10)	<0.001	0.48 (0.14)	0.46 (0.13)	0.289
Starting dose, mg/day, median (IQR)	100 (100–100)	100 (100–100)	<0.001	50 (50–100)	100 (50–100)	0.147
Follow-up time, days, median (IQR)	371 (163–657)	379 (194–652)	0.506	295.5 (70.5–614.5)	270 (95–565)	0.996
Allopurinol dose at time of switch to benzbromarone, mg/day	N/A	N/A	N/A	173.61	221.54	0.686[c]
Allopurinol dose at time of adding benzbromarone, mg/day	N/A	N/A	N/A	216.67	334.29	0.097[c]

[a]The P-values for categorical variables were calculated by χ^2 analysis; for continuous variables, the appropriate (non-)parametric analysis was used, based on Gaussian distribution. [b]Missing data in some patients. [c]After correction for baseline serum uric acid, renal function and age. eGFR: estimated glomerular filtration rate; IQR: interquartile range; N/A: not assessed.

Fɪɢ. 1 Kaplan–Meier curve for time to reach the target at any time during follow-up
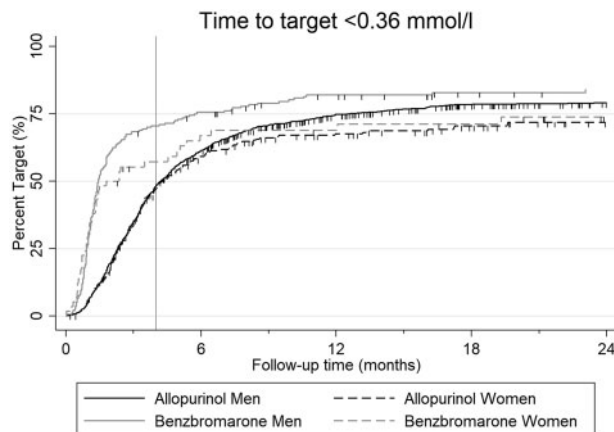
Time to reach target 0.36 mmol/l (any time during follow-up)

Figure 1 shows the Kaplan–Meier curves for time to reach target. During the first 120 day period, both women and men using benzbromarone reached the target sUA faster compared with using allopurinol (for women, HR 2.74; 95% CI: 1.70, 4.43; and for men, HR 2.78; 95% CI: 2.16, 3.59). The time to reach the target sUA was not significantly different in women compared with men for both allopurinol and benzbromarone: HR 0.95 (95% CI: 0.81, 1.11) and HR 0.93 (95% CI: 0.57, 1.52), respectively.

For the period after 120 days, for both women and men the HRs were inversely lower for benzbromarone compared with allopurinol: HR 0.57 (95% CI: 0.34, 1.06) and HR 0.57 (95% CI: 0.38, 0.86) for women and men, respectively. Again, corrected for confounding, sex was not an effect modifier of the difference in the time to reach the target sUA for allopurinol and benzbromarone during follow-up (HR 0.98; 95% CI: 0.60, 1.61).

ULT dose at target serum uric acid <0.36 mmol/l

The mean dose of allopurinol at the time of reaching the target sUA was lower in women compared with men, 216 mg and 271 mg, respectively (difference −55 mg; 95% CI: −73, −37). After correction, this difference remained statistically significant, at −45 mg (95% CI: −67, −23). The mean dose of benzbromarone at the target sUA was similar for women and men: 86 mg and 88 mg, respectively (difference −2 mg; 95% CI: −15, 11). After correction, this difference was 4 mg (95% CI: −9, 18). For the subset of patients using benzbromarone in addition to allopurinol, mean doses were similar for women and men at the time of reaching the target sUA.

Discussion

Our results show that, although women have lower urate excretion than men [10, 11], this does not translate into relevant differences between women and men in response rates to an XO inhibitor or a uricosuric drug. Therefore, the choice of urate-lowering drug does not have to be based on the supposed sex differences.

Three interesting additional findings were observed. Firstly, the time to reach the sUA target for benzbromarone compared with allopurinol was significantly shorter. Secondly, more men on benzbromarone reached the sUA target within 6 months than on allopurinol. Thirdly, women reached the sUA target at a lower mean allopurinol dose than men.

Starting with the first observation, there are several explanations for the more swift response to benzbromarone. Firstly, this might be caused by the lower baseline sUA before the start of benzbromarone, because this treatment is often given as an add-on to allopurinol. However, this was accounted for in the analyses. Also, benzbromarone is often started at a higher dose relative to its maximum dose than allopurinol. Another reason for this finding might be that benzbromarone is a more potent drug with regard to sUA lowering. Renal handling of uric acid plays a key role in the pathophysiology of gout in most patients [16]. Given that benzbromarone inhibits uric acid reabsorption, it provides a more logical pharmacological approach to hyperuricaemia in most patients. When using this drug in clinical practice, this faster response should be taken into account when using this drug in a treatment strategy. The second finding follows the same reasoning as the first, with the statistically significant difference possibly found only in men because of the smaller sample of women in our cohort.

Regarding the third finding, the lower effective allopurinol dose in women might be caused by residual confounding; for example, BMI was not corrected owing to a large number of missing values. Another reason might be different pharmacokinetic or pharmacodynamic effects in women compared with men. Unfortunately, reliable subgroup analyses by sex are very rare in existing allopurinol studies because the proportion of women is often 10% or less. In a previous study looking at the efficacy of febuxostat and allopurinol in women using data

from three randomized controlled trials, only 226 women of the >4000 patients were included [7].

Strengths of this study include a relatively large population of both sexes, especially women, and comparison between allopurinol and benzbromarone, a drug for which data are relatively scarce. Although the latter might also limit generalizability, our goal was to make a comparison between an XO inhibitor with a uricosuric drug in light of the lower sUA excretion in women. Although benzbromarone is not used worldwide, newer uricosuric drugs have been developed and marketed recently. Considering the same working mechanism, we hypothesize that other uricosuric drugs might have similar effects to benzbromarone, making this a comparison of interest. Our cohort is considered to be a good representation of gout patients in secondary rheumatology care because the male-to-female ratio, patient and disease characteristics and the differences in these characteristics between women and men are comparable to previous studies in secondary care [3–5]. Limitations of our study are, firstly, the retrospective design, mostly attributable to incomplete outcome assessment. This is also the reason why we chose to use the sUA target instead of flare incidence, because the former is better assessed in this study. Also, nearly all patients who used benzbromarone previously failed allopurinol, and this might result in biased efficacy estimates for benzbromarone and for the comparison between allopurinol and benzbromarone. However, this should not hamper comparison between sexes, also because we used cluster variance analyses to account for interdependence.

In conclusion, this study did not demonstrate between-sex differences regarding the response to either a uricosuric agent or an XO inhibitor, negating different treatment choices by sex.

Acknowledgements

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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