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ORIGINAL RESEARCH ARTICLE

Role of Community Pharmacies for the Detection of Potentially Inappropriate Xanthine Oxidase Inhibitor Prescriptions

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Abstract

Background Xanthine oxidase (XO) inhibitors are largely the treatment of choice for gout, but allopurinol is often inappropriately used for asymptomatic hyperuricemia. There is little evidence that allopurinol is useful in preventing cardiovascular diseases and therapeutic decisions must the balance the expected benefit with the potential harm.

Objective To investigate the appropriateness of XO inhibitor use in relation to evidence-based indications and examine the role of community pharmacies in the detection of inappropriate prescriptions of these drugs.

Methods This is an observational study conducted in eight community pharmacies. Each pharmacist was asked to interview a sample of patients who had received prescriptions of XO inhibitors. Patients were asked to complete a structured minimum data set that collected information on drug indication, history of gout, and presence of cardiovascular diseases.

Results The study sample included 74 patients receiving XO inhibitors. About one third of patients reported being treated for asymptomatic hyperuricemia and had never had a gout attack. About half of the patients treated for asymptomatic hyperuricemia had been receiving the drug treatment for more than 3 years. Four asymptomatic hyperuricemic patients received allopurinol to treat hypertension. Among the patients treated for asymptomatic hyperuricemia, there was a higher presence of diabetes mellitus, obesity, previous myocardial infarction, and heart failure than in patients treated for an appropriate indication.

Conclusions Inappropriate use of XO inhibitors is principally related to the treatment of hyperuricemia in patients with cardiovascular diseases. Community pharmacists have a central role in pharmacovigilance, by contributing to the prevention and identification of potentially inappropriate drug prescriptions.

Members of Study Group of Community Pharmacists (SGCP) Investigators are listed in Appendix.

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Key Points

Xanthine oxidase (XO) inhibitors are largely the treatment of choice for gout, but allopurinol is often inappropriately used for asymptomatic hyperuricemia. There is little evidence that allopurinol is useful in preventing cardiovascular diseases and therapeutic decisions must balance the expected benefit with the potential harm.

In Italy, allopurinol is not prescribed according to guidelines, thus exposing patients to an increased risk of adverse drug reactions. Inappropriate use of XO inhibitors is principally related to the treatment of hyperuricemia in patients with cardiovascular diseases, although there is little evidence that allopurinol is useful in preventing cardiovascular diseases.

Community pharmacies could contribute to the prevention and identification of potentially inappropriate drug prescriptions.

Introduction

Xanthine oxidase (XO) inhibitors are the principal treatment of choice for gout, and allopurinol is used by more than 1.2 million patients in the USA and UK. However, this drug is often inappropriately used in asymptomatic hyperuricemia [1], and this indication is not supported by conclusive evidence from prospective, randomized, clinical human research trials, nor is it recommended by any guidelines [2]. The culprit in gout is the accumulation of uric acid in joints. Uric acid is formed mainly by the enzyme XO, which converts hypoxanthine and oxygen into uric acid, superoxide, and other oxidative-free radicals [3]. It is therefore clear that inhibiting XO will reduce uric acid and, hence the tendency for gout [4]. Inhibition of XO and the consequent production of harmful oxidative metabolites has been associated with other clinical benefits of allopurinol: improvement in endothelial/vascular dysfunction; reduction of vascular tissue oxidative stress; increase in adenosine triphosphate/energy, and oxygenation of ischemic tissues [3]. Allopurinol has therefore been suggested to be potentially useful in different conditions: prevention or regression of atherosclerosis; prevention of cardiovascular (CV) events in patients after an acute coronary syndrome or myocardial infarction, transient ischemic attack, cerebral vascular accident, or intermittent claudication, and reduction of heart failure after myocardial infarction [5]. However, there is little evidence for a role of allopurinol in the prevention of CV diseases and the debate on its role in asymptomatic hyperuricemic patients is still open. Only two epidemiologic and experimental studies (one in patients with heart failure and one in hyperuricemic patients) have suggested a link between hyperuricemia, hypertension, and reduced total mortality [6, 7], and two small randomized controlled trials found that allopurinol reduced CV events [8, 9]. However, treating asymptomatic hyperuricemia has no clear benefit because allopurinol hypersensitivity syndrome is rare and often occurs as a consequence of inappropriate drug use [10]. Therapeutic decisions must therefore balance the expected benefit with the potential harm.

Similarly, febuxostat is a new, potent non-purine-selective inhibitor of XO and is now recommended as the first-line pharmacologic urate-lowering therapy for gout in the American College of Rheumatology guidelines [2]. However, although it achieves more selective, potent, and persistent XO inhibition and greater hypouricemic activity than allopurinol, there is no evidence of CV benefits [11].

According to the hypothesis that inappropriate prescription is associated with the treatment of asymptomatic hyperuricemia in patients with CV diseases, and considering the licensed indications for XO inhibitors (management of signs and symptoms of primary or secondary gout; chemotherapy-induced hyperuricemia; and recurrent calcium oxalate stones), we conducted an observational study among Italian community pharmacies to examine the role of pharmacists in the detection of inappropriate prescriptions of these drugs.

Methods

Study Design

This study was conducted in Italy between January and May 2014 among eight community pharmacies distributed in six different regions. The Study Group of Community Pharmacists (SGCP) involved eight pharmacists participating with an academic master in clinical pharmacies. The project was divided into two parts: study design and experimental. During the first part of the study the pharmacists received training for carrying out the project, including a standardized procedure for the interviews. Each pharmacist was asked to interview at least one patient (the first one with a XO inhibitor prescription) for each week of the study period. Only users of the drug dispensed were considered eligible for the study. Patients who met the inclusion criteria were interviewed with a structured ad hoc questionnaire with predefined answers at the moment of drug dispensation. The questionnaire was developed with a structured consensus development process that included: evaluation of the evidence; discussion and debate among

all members; and definition of issues to be investigated. The consensus process involved two researchers (with expertise in clinical pharmacology, drug information, and evidence evaluation) and the community pharmacists involved in the study, leading to the definition of the ad hoc questionnaire (see Supplementary Material online).

The pharmacists then completed a standardized, web-based Case Report Form developed to collect data from all of the pharmacists involved in the study and facilitate data analysis. Data collected included sociodemographic details, drug indication, dosage, body mass index, risk factors for hyperuricemia (alcohol consumption and red meat), time since the last gout attack, level of serum uric acid before drug treatment, duration of drug prescription, presence of CV diseases, and prescriptions of drugs with potentially severe drug–drug interactions. All data were self-reported by the patient and no information was extracted from a health record completed by the physician. Only patients who refused the interview were excluded by the study. No refusal was registered. Data collection complied fully with Italian laws on personal data protection and required no ethical committee approval under the applicable legal principles on patient registries.

Diseases and Drug Appropriateness

The prescription of allopurinol or febuxostat was considered appropriate according to licensed indications for XO inhibitors, which include managing the signs and symptoms of primary or secondary gout, including gouty nephropathy, uric acid nephrolithiasis, and other specified manifestations such as tophi [12]. We also considered the prescription of allopurinol appropriate in patients with chemotherapy-induced hyperuricemia. Patients treated for hyperuricemia but who had no history of a gout attack, chemotherapy-induced hyperuricemia, or calcium oxalate stones were considered to be treated for asymptomatic hyperuricemia. Hyperuricemia was defined as a level of serum uric acid before drug treatment that was higher than 5.7 mg/dL for women and 7 mg/dL for men.

Statistical Analysis

The sociodemographic characteristics of patients were described using a univariate analysis (with mean or percentage values). Differences in means were tested using the two-tailed unpaired Student's t test and the Pearson Chi-square test for categorical variables. Analyses were done with JMP Pro 11 (SAS Institute Inc., Cary, NC, USA). p values less than 0.05 were considered statistically significant.

Results

The study sample included 74 patients receiving XO inhibitors. About one third of patients reported a lack of gout history and had to be treated for asymptomatic hyperuricemia. No patient was treated for antineoplastic-induced hyperuricemia. Table 1 summarizes sociodemographic characteristics of patients interviewed and the indication of drug treatment. Allopurinol was the XO inhibitor most frequently prescribed. Febuxostat was prescribed to nine patients: in three patients with a history of gout, in two patients with uric acid nephrolithiasis, and in four patients with asymptomatic hyperuricemia. Febuxostat was prescribed for an expected better efficacy and tolerability than allopurinol in four patients never treated with allopurinol: two patients with asymptomatic hyperuricemia, one patient with gout, and one patient with uric acid nephrolithiasis.

Twenty-five patients were treated for an unlicensed indication, reporting to receive the XO inhibitor for asymptomatic hyperuricemia and in four patients also for hypertension. Among these patients, information about serum uric acid levels before treatment was available for eight male patients: in six patients, the level of serum uric acid was 7.7–8.2 mg/dL, while in the other two patients the range was 6.2–6.6 mg/dL. About half of the patients treated for asymptomatic hyperuricemia had received the drug treatment for more than 3 years. The duration of XO treatment is described in Table 2. Patients with asymptomatic hyperuricemia have a higher presence of diabetes mellitus, obesity, previous myocardial infarction, and heart failure than patients with an appropriate indication, although differences were not statistically significant (Table 3). The interview of each patient took approximately 10 min.

Table 1 Main sociodemographic characteristics of patients receiving xanthine oxidase inhibitors and drug indications

Variable	Value
Patients (n)	74
Age, years, mean (range)	74 (36–98)
Male (%)	43 (58.1)
Patients receiving allopurinol (%)	65 (87.8)
Indication for drugs (%)	
Gout	45 (60.8)
Uric acid nephrolithiasis	4 (5.4)
Asymptomatic hyperuricemia[a]	25 (33.8)

[a] All patients had no history of a gout attack

Table 2 Distribution of patients receiving xanthine oxidase inhibitors according to indication and duration of treatment

Duration of treatment	Number of patients for drug indication (%)		
	Gout ($n = 45$)	Uric acid nephrolithiasis ($n = 4$)	Asymptomatic hyperuricemia ($n = 25$)
<3 month	3 (6.7)	1 (25.0)	5 (20.0)
3 month to 1 year	3 (6.7)	–	4 (16.0)
1–3 years	12 (26.7)	–	4 (16.0)
>3 years	27 (60.0)	3 (75.0)	12 (48.0)

Discussion

Our study found that community pharmacies could play an important role in the detection of inappropriate drug prescriptions, suggesting that observational studies conducted in the community pharmacies could be useful to identify inappropriate drug use. We found that about one third of patients receiving XO inhibitors were treated for asymptomatic hyperuricemia and had at least one CV disease, suggesting an association between inappropriate prescription of XO inhibitors and the presence of CV diseases in hyperuricemic patients. These results are of particular concern because there is little evidence that allopurinol is useful in preventing CV diseases [10].

Our findings confirm the results of a recent Italian study conducted in internal medicine and geriatric wards, which found that among 4,035 older patients admitted and 3,502 patients discharged only 8.6 and 9.4 % of patients receiving XO inhibitors were appropriately treated at admission and discharge, respectively. The study also found that inappropriate use of XO inhibitors was principally related to the treatment of asymptomatic hyperuricemia and various CV diseases [13]. Although conducted in a different setting with a different population and the differences between the characteristics of patients with appropriate indication and asymptomatic hyperuricemia were not statistically significant, we found a high rate of inappropriate prescription of XO inhibitors for unlicensed indications.

It has been suggested that allopurinol could be of benefit in primary prevention of hypertensive and diabetic patients, especially those with left ventricular hypertrophy, and in secondary prevention, for acute and chronic myocardial ischemia, renal failure, cerebral vascular accident, transient ischemic attack or peripheral artery disease, and heart failure [14]. Although allopurinol can improve the key surrogates of endothelial dysfunction, vascular oxidative stress, myocardial ischemia, and left ventricular mass, and the pharmacological effects look extremely promising, no prospective randomized clinical trials have shown CV benefits in either primary or secondary prevention.

Table 3 Characteristics of patients with appropriate and non-appropriate indication of xanthine oxidase inhibitors

	Appropriate indication[a]	Asymptomatic hyperuricemia	*p* value
n	49	25	
Age, years, mean (range)	75 (36–98)	71 (37–89)	0.13
Male (%)	26 (53.1)	17 (68.0)	0.27
Mean daily dose of allopurinol, mg[b]	250	200	0.22
Patients treated with 300 mg/day, *n* (%)	31 (63)	8 (32)	
Patients treated with 150 mg/day, *n* (%)	11 (22)	10 (40)	
Patients treated with 100 mg/day, *n* (%)	2 (4)	2 (8)	
Dosage not reported	–	1 (4)	
Mean daily dose of febuxostat, mg[b]	80	150	0.19
Patients treated with 150 mg/day, *n* (%)	–	1 (4)	
Patients treated with 80 mg/day, *n* (%)	4 (8)	–	
Dosage not reported	1 (2)	3 (12)	
Consumption of alcohol	16 (32.7)	12 (48.0)	0.20
Consumption of red meat (>3 times a week)	9 (18.4)	2 (8.0)	0.22
Hypertension (%)	41 (83.7)	17 (68.0)	0.13
Diabetes mellitus (%)	13 (26.5)	9 (36.0)	0.40
Hypercholesterolemia (%)	17 (34.7)	7 (28.0)	0.56
Obesity (%)	11 (22.4)	6 (24.0)	0.81
Previous myocardial infarction (%)	4 (8.2)	4 (16.0)	0.32
Heart failure (%)	2 (4.1)	2 (8.0)	0.49
At least two cardiovascular diseases[c]	21 (42.8)	12 (48.0)	0.67

[a] Gout or uric acid nephrolithiasis

[b] Excluding patients with missing information

[c] Including diabetes mellitus

Furthermore, whether lowering serum uric acid will lower blood pressure remains an unanswered question. Data on pharmacotherapy for hyperuricemia in hypertension are limited and restricted to adolescents with recently diagnosed, mild essential hypertension [15]. A recent Cochrane review suggests that there is insufficient evidence to recommend the use of allopurinol or other hypouricemic drugs for initial or adjuvant treatment of hypertension and more randomized clinical trials are needed [16]. In addition, two recent, genetic, large prospective cohort studies found no strong evidence for causal relations between uric acid and ischemic heart disease or blood pressure. However, a causal effect was found between body mass index, uric acid level, and hyperuricemia, suggesting that the body mass

index can act as a confounder in observational associations and in the development of uric acid-related conditions [17].

Because the information on allopurinol inappropriate prescription and its consequences is still scant, continuous surveillance and specific recommendations on appropriate use could help optimize urate-lowering therapy, targeting treatment to those who stand to benefit and avoiding treatment for those who will not [18]. A recent paper from the Lombardy (Italy) Center for Pharmacovigilance showed that out of 10 cases of adverse reactions to allopurinol reported from September 2012 to September 2013, seven were severe skin reactions, including Stevens–Johnson syndrome, and one patient died. In all cases, allopurinol was not necessary based on current guidelines for the treatment of asymptomatic hyperuricemia and gout [18]. In addition, a case of rhabdomyolysis was recently reported following the administration of febuxostat for hyperuricemia to a patient with chronic kidney disease [19]. Bearing in mind that about 5 % of the population and a quarter of hospitalized patients are hyperuricemic, most of whom are asymptomatic and will never develop gout, the treatment of asymptomatic hyperuricemia must be considered with extreme caution because inappropriate treatment is clearly unacceptable [10].

Community pharmacies have several roles in promoting appropriate drug prescriptions: the role of a clinical pharmacist in medication review has been clearly demonstrated in older patients who receive repeat prescriptions, where a pharmacist review of medications resulted in more prescription changes, fewer medications prescribed, and lower medication costs than did usual general practice [20, 21]. In England, community pharmacists can provide a wide range of advanced pharmaceutical services, which include medicine use reviews, anticoagulant monitoring services, disease-specific medicine management services, and many others. This suggests that pharmacists can be effective in providing benefits across the range of pharmaceutical care and even in economic terms [22]. The role in promoting patient reporting of adverse drug reactions has been demonstrated by an Italian study conducted among 118 community pharmacies in Veneto [23]. Our study also suggests that observational studies conducted in community pharmacies could contribute to the pharmacovigilance activity of identifying signals of potentially inappropriate drug prescriptions and advising physicians to reconsider the prescription of the drug according to the licensed indication. Collaborative interventions with general practitioners are, in fact, essential to promote and improve appropriate drug use. This was recently suggested by a cluster randomized trial of 303 older long-term users of benzodiazepines recruited from 30 community pharmacies in Canada, where community pharmacies contributed to promote direct patient education to reduce inappropriate prescriptions of benzodiazepines in older patients [24].

Limitations of the present study include the small number of patients interviewed and the lack of data about uric acid levels before the treatment of some hyperuricemic patients, which limits the possibility of evaluating the use of allopurinol in patients with asymptomatic hyperuricemia with a conditional benefit, such as those with persistent high uric acid level (above 13 mg/dL in men or 10 mg/dL in women), for the nephrotoxic risks of uric acid [25], or in those with urinary uric acid excretion exceeding 1,100 mg daily, which has been associated with a 50 % increase in the risk of uric acid calculi [26, 27]. Although this limitation tends to underestimate the appropriate prescription of XO inhibitors, for the majority of patients with hyperuricemia allopurinol is not justified by current evidence [1, 16]. Although our study cannot establish with certainty a causal relationship between CV diseases and allopurinol prescription, it does suggest a potential association between allopurinol prescription and the presence of CV diseases in which clinical benefits of allopurinol are expected. Another limitation of the study is the lack of data about patients with severe adverse drug reactions of allopurinol, which cannot be identified because we interviewed only patients receiving treatment.

Conclusions

Inappropriate use of XO inhibitors is mainly related to the treatment of asymptomatic hyperuricemia in patients with no history of gout. Careful assessment of clinical conditions and stricter adherence to evidence-based guidelines are essential for rational use. Community pharmacists could contribute to the quality use of drugs, to help consumers better manage their medicine and could have a great role in identifying signals of potential inappropriate drug prescriptions. Collaboration between physician and pharmacists has to evolve in the interest of the quality use of medicines and improved health outcomes.

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Conflicts of interest The authors have no conflict of interest.

Appendix

Community Pharmacists and co-authors of the Study Group of Community Pharmacist (SGCP) are as follows:

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Statistics Codjo Djignefa Djade (IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", Milano).

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