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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Inappropriate prescription of allopurinol and febuxostat and risk of adverse events in the elderly: results from the REPOSI registry

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Abstract
Purpose To investigate the prevalence of xanthine oxidase (XO) inhibitors prescription at admission and discharge in elderly hospital in-patients, to analyze the appropriateness of their use in relation to evidence-based indications, to evaluate the predictors of inappropriate prescription at discharge and the association with adverse events 3 months after hospital discharge.
Methods This cross-sectional study, based upon a prospective registry, was held in 95 Italian internal medicine and geriatric hospital wards. The sample included 4035 patients aged 65 years or older at admission and 3502 at discharge. The prescription of XO inhibitors was considered appropriate in patients with diagnosis of gout, gout nephropathy, uric acid nephrolithiasis, tophi, and chemotherapy-induced hyperuricemia. In order to evaluate the predictors of inappropriate prescription of XO inhibitors, we compared the characteristics of patients considered inappropriately treated with those appropriately not treated.
Results Among the 4035 patients eligible for the analysis, 467 (11.6 %) were treated with allopurinol or febuxostat at hospital admission and 461 (13.2 %) among 3502 patients discharged. At admission, 39 (8.6 %) of patients receiving XO inhibitors and 43 (9.4 %) at discharge were appropriately treated. Among those inappropriately treated, hyperuricemia, polytherapy, chronic renal failure, diabetes, obesity, ischemic cardiomyopathy, heart failure, and cardiac dysrhythmias were associated with greater prescription of XO inhibitors. Prescription of XO inhibitors was associated with a higher risk of adverse clinical events in univariate and multivariate analysis.
Conclusions Prevalence of inappropriate prescription of XO inhibitors remained almost the same at admission and discharge. Inappropriate use of these drugs is principally related to treatment of asymptomatic hyperuricemia and various cardiovascular diseases.

Keywords Aged · Pharmacoepidemiology · Allopurinol

REPOSI stands for Registry of Polytherapies SIMI (Società Italiana di Medicina Interna)

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Background

In the occurrence of gout, the culprit is the accumulation in joints of uric acid, mainly formed by the enzyme xanthine oxidase (XO) which converts hypoxanthine into uric acid, superoxide, and other oxidative-free radicals. XO inhibitors are the treatment of choice for gout, and allopurinol is used by more than 1.2 million patients in the USA and UK. Inhibition of XO by allopurinol has been suggested to be associated to various clinical benefits: improvement of endothelial dysfunction, reduction of vascular tissue oxidative stress, increase in ATP energy, and oxygenation of ischemic tissues [1]. Accordingly, allopurinol has been considered potentially useful in an array of conditions other than gout: prevention or regression of atherosclerosis [2], prevention of cardiovascular disease (CVD) in patients who had had an acute coronary syndrome (ACS) or myocardial infarction (MI), transient ischemic attacks (TIA), cerebral vascular accidents (CVA), intermittent claudication, and heart failure after MI. However, little evidence supports a role of allopurinol in the prevention of CVD and there is still an open debate regarding its role in asymptomatic hyperuricemia, because only two epidemiological and experimental studies (in heart failure and hyperuricemia) suggested a link between hyperuricemia, hypertension, and lower total mortality [3, 4], and only two small randomized controlled trials showed that allopurinol reduces the incidence of CVD [5, 6]. On the other hand, the allopurinol hypersensitivity syndrome is rare but often occurs as a consequence of inappropriate treatment with this agent [7], so that therapeutic decisions should take into account the balance between expected benefits and potential harms. Febuxostat, a new potent non-purine-selective inhibitor of XO, is now recommended as the first-line urate-lowering therapy for gout jointly with allopurinol according to the American College of Rheumatology guidelines [8]. Although this drug provides more selective, potent and persistent inhibition of XO and greater hypouricemic activity than allopurinol, there is no evidence for its benefits in CVD [9].

With this background 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), because little is known on the appropriateness of prescription of XO inhibitors in elderly patients hospitalized, we used REPOSI, a registry stemming from a network of Italian internal medicine and geriatric wards, in order to investigate the rate of allopurinol and febuxostat prescription at hospital admission and discharge in the elderly. Other goals were the analysis of appropriateness in relation to evidence-based drug indications, the predictors of inappropriate prescription, and its association with the risk of adverse clinical events, re-admission, and all-cause mortality 3 months after hospital discharge. For the purpose of the study, the prescription of XO inhibitors was considered appropriate in patients with diagnosis of gout, gout nephropathy, uric acid nephrolithiasis, tophi, and chemotherapy-induced hyperuricemia.

Methods

Data collection

The Registro Politerapie SIMI (REPOSI) is a collaborative and independent, initiative of the Italian Society of Internal Medicine (SIMI), the IRCCS Istituto di Ricerche Farmacologiche Mario Negri and the IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation. The registry was set up in 2008 from a network of internal medicine and geriatric wards in order to collect information on hospitalized elderly patients with multimorbidities receiving multiple drugs. The first run of data collection was between January and December 2008, the second between January and December 2010, and the third between January and December 2012. To ensure an unselected population of elderly patients admitted to internal medicine wards, during four-week period, 3 months apart, the first ten patients admitted to the wards participating in the study were consecutively recruited if they were 65 years old or older. Participation was voluntary and all patients gave signed informed consent. Data collection complied fully with the Italian laws on personal data protection and Ethical Committees of each ward participating to REPOSI approved the study. The attending physicians completed a standardized web-based case report form, including diagnosis at hospital admission, sociodemographic details and drug treatment at admission, during hospital stay and at discharge. In the second and third REPOSI runs, we decided to collect additional information and to do a short-term follow-up in order to improve the quality of data: main laboratory parameters, comorbidity according to the Cumulative Illness Rating Scale (CIRS) (Pamellee), basic activities of daily living, cognitive impairment, depression, and clinical events during hospital stay. Patients were then followed 3 months after discharge by means of a telephone interview in order to collect information on new diagnoses, hospital re-admissions, drug regimens, adverse events, and basic activities of daily living.

To establish the rate of potentially inappropriate XO inhibitor prescriptions, we considered all patients recruited in REPOSI, excluding only those who died in hospital or were transferred to another ward during hospitalization. To better evaluate the related risk of adverse clinical events, re-admission and all-cause mortality, we considered only patients recruited in the second and third REPOSI run who had completed the 3-month follow-up. Of the 2318 in-patients discharged from hospital, follow-up data were not available for 585 (25 %), for various reasons: death before hospital discharge, transfer to another ward, refusal of the 3-month

telephone interview, and discharge in critical conditions (life expectancy less than 3 month) or logistic reasons.

Diseases and drug appropriateness

Prescription of allopurinol or febuxostat was considered appropriate according to the presence of gout (including gout nephropathy), uric acid nephrolithiasis, and other manifestations like tophi (IDC-9 code 274). We also considered appropriate the prescription of allopurinol in patients with a diagnosis of chemotherapy-induced hyperuricemia (ICD-9 code 140–239 and diagnosis of hyperuricemia). The prescription of XO inhibitors was considered inappropriate in patients without the forementioned conditions. Dosage of XO inhibitors was not considered as criteria of drug appropriateness because this information was not collected. Diagnoses were derived by ICD-9 codes and personal interviews. In order to evaluate the predictors of inappropriate prescription of XO inhibitors, we compared the characteristics of patients considered inappropriately treated with those appropriately not treated (Fig. 1).

Outcomes

In order to evaluate the risk of adverse clinical events from discharge to the time of follow-up examination, re-admission, and all-cause mortality associated with inappropriate use of XO inhibitors, we considered eligible for this analysis only the patients with complete follow-up data. Information on re-admission and survival of the patients was obtained after 3 months.

Statistical analysis

Analysis of variance was used to evaluate the relationship between potentially inappropriate use of XO inhibitors and incidence of adverse clinical events, re-admission, and mortality. Multivariate analyses were adjusted for age, sex, and possible confounders for CVD benefit of XO inhibitors. Analyses were done with JMP Pro 10 (SAS Institute Inc.).

Results

XO inhibitors were prescribed to 467 patients (11.6 %) among 4035 admitted to hospital and to 461 (13.2 %) among those discharged (3502). The mean number of drugs used and diagnoses were higher in patients given XO inhibitors than in those not treated (Table 1). Allopurinol was the most frequently prescribed XO inhibitor, only two patients at admission and two at discharge receiving febuxostat. At admission, only 39 patients (8.4 % of those receiving a XO inhibitor) and 43 at discharge (9.3 %) were appropriately treated; 428 patients (91.6 %) and 418 (90.7 %) were inappropriately treated at admission and discharge, respectively. Furthermore, 286 patients (66.8 % of patients inappropriately treated at admission) received a XO inhibitor inappropriately both at admission and discharge and only in 74 of them (17.3 % of patients inappropriately treated at admission) these drugs were appropriately withdrawn at the time of hospital discharge. In addition, among patients appropriately not treated at admission, the drug was inappropriately prescribed at discharge to 130 (31.1 % of patients inappropriately treated at discharge). The mean duration of XO inhibitor treatment was 3.3 years (interquartile range 0.9–8.3 years, data available for 130 patients). Allopurinol was also inappropriately prescribed to five patients discharged in critical conditions.

Predictors of inappropriate prescription of XO inhibitors at discharge were evaluated by comparing the cohort of patients inappropriately treated (n=418) with those appropriately not treated (n=3,024). Among patients inappropriately treated, asymptomatic hyperuricemia, therapy with multiple drugs, chronic renal failure, diabetes, obesity, ischemic heart disease, heart failure, and cardiac arrhythmias were associated with greater prescription (Table 2). All these variables were independently associated with greater use of XO inhibitors in a multivariate model, adjusted for all the variables considered in the univariate model (data not shown).

The cohort of patients inappropriately treated and those appropriately not treated at discharge, which allowed to evaluate the association between XO inhibitors prescription and clinical outcomes at 3-month follow-up, included 2274 subjects and follow-up was available for 1697 (74.6 %). In them, prescription of XO inhibitors was associated with a higher risk of adverse clinical events, while no difference was found for the risk of re-hospitalization and all-cause mortality. Results were confirmed by multivariate analysis adjusted for age, sex, hyperuricemia, hypertension, diabetes, ischemic heart disease, heart failure, and cardiac arrhythmia (Table 3). Glomerular filtration rate (GFR) at discharge (estimated using the CKD-EPI Creatinine Equation) was available for 1570 patients. Multivariate analysis adjusted for all previous covariates and GFR<30 ml/min/1.73 m [2] found similar results for adverse clinical events (odds ratio (OR) 1.94; 95 % confidence interval (CI), 1.21–3.06; p=0.0067), re-admission (OR 0.67; 95 % CI, 0.43–1.00; p=0.052), and mortality (OR 1.20; 95 % CI, 0.68–2.02; p=0.52).

Discussion

This study provides a picture of elderly people with multimorbidity and polypharmacy currently treated in internal medical hospital wards with XO inhibitors, mainly allopurinol: approximately, 10–12 %, a prevalence similar to that observed in elderly patients living at home in New Zealand

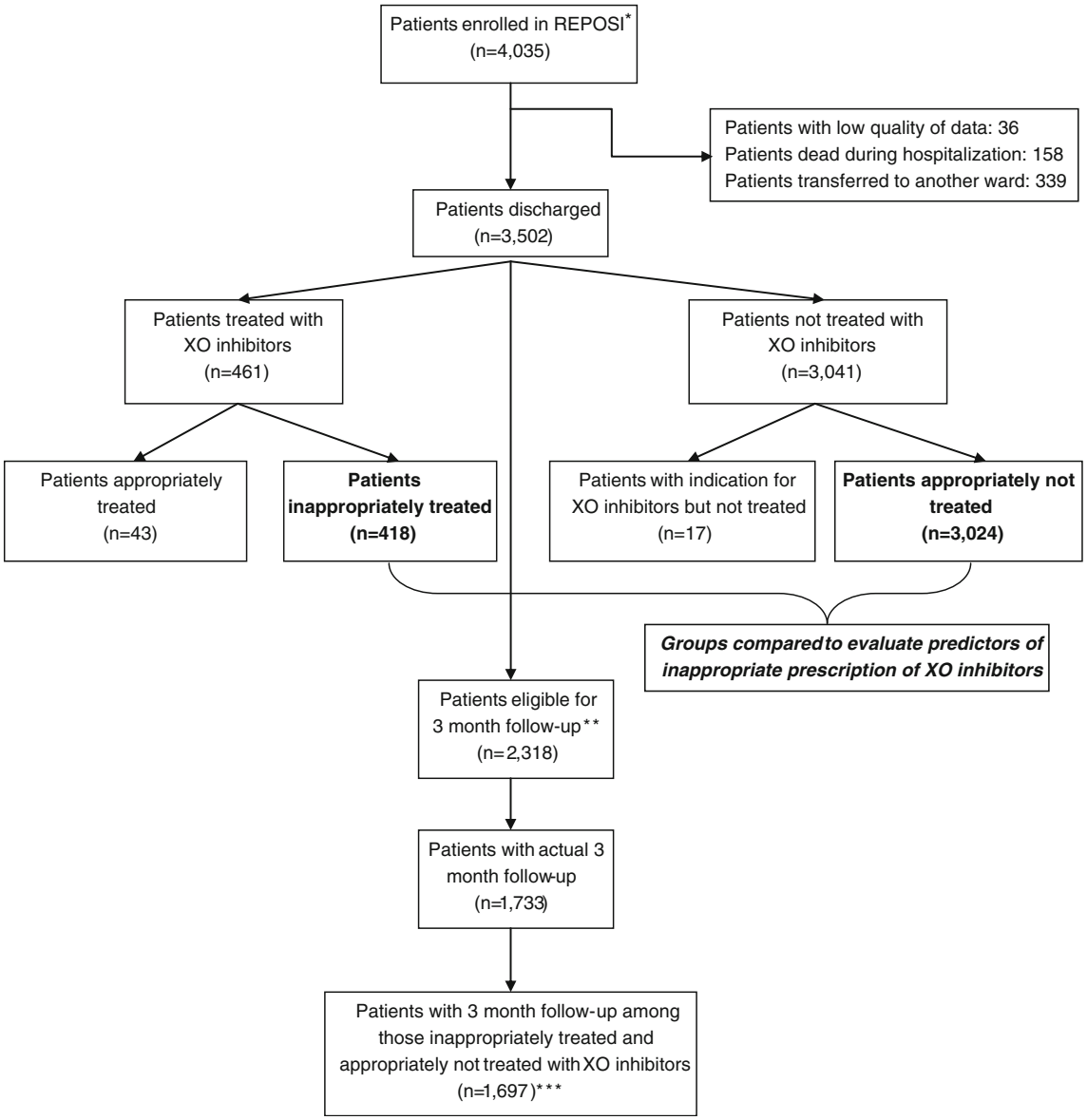

Fig. 1 Flow chart of the study

(9 % among patients between 65 and 74 years and 8 % above 75 years) [10]. Hospital admission and discharge were both associated with a high prevalence of inappropriate prescription of allopurinol, mainly related to the management of hyperuricemia and various CVD. The observation that hospitalization was not associated with a reduction in the inappropriate use of allopurinol, particularly in hyperuricemic patients, is of special concern, because in this setting, confirmation of the inappropriate prescription did stem from expert hospital internists.

Table 1 Main characteristic of patients treated with xanthine oxidase (XO) inhibitors

	At admission (n=4,035)		At discharge (n=3,502)	
	Treated	Not treated	Treated	Not treated
Total	467	3,568	461	3,041
Age, years (mean±SD)	79.5±7.0	79.2±7.5	79.0±7.1	79.1±7.5
Women (%)	39.5	53.4	41.4	54.0
Drugs, no (mean±SD)	7.9±2.7	4.9±2.7	8.5±2.9	5.9±2.8
Diagnoses, no (mean±SD)	6.6±2.8	5.1±2.7	7.4±2.7	6.1±2.7

Table 2 Predictors of inappropriate prescription of XO inhibitors at discharge

	Inappropriately treated	Appropriately not treated	OR (95 % CI)	*p*
n	418	3,024		
Drugs, no (mean±SD)[a]	7.5±2.9	5.9±2.8		<0.0001
Age (years±SD)	79.0±7.0	79.1±7.5		0.50
Male (%)	57.7	46.0	1.60 (1.30–1.97)	<0.0001
Obesity (%)	6.0	3.2	1.94 (1.23–3.05)	0.007
Hypercholesterolemia (%)	8.9	11.3	0.76 (0.53–1.09)	0.12
Hypertension (%)	75.4	67.8	1.45 (1.15–1.84)	0.001
Diabetes (%)	39.7	26.5	1.83 (1.48–2.26)	<0.0001
Ischemic cardiomyopathy (%)	28.2	19.6	1.61 (1.28–2.03)	<0.0001
Heart failure (%)	34.0	16.3	2.63 (2.11–3.30)	<0.0001
Cardiac dysrhythmias (%)	36.1	25.1	1.69 (1.36–2.09)	<0.0001
Chronic renal failure (%)	43.8	13.3	5.06 (4.07–6.31)	<0.0001
Asymptomatic hyperuricemia (%)	7.5	0.4	18.62 (9.66–35.9)	<0.0001
Hypertension+ischemic cardiomyopathy+heart failure (%)	7.3	3.0	2.53 (1.65–3.88)	<0.0001
Hypertension+diabetes+ischemic cardiomyopathy+heart failure (%)	3.2	1.4	2.29 (1.22–4.30)	0.02
Polytherapy[a] (%)	87.1	66.9	3.33 (2.48–4.47)	<0.0001

[a] Prescription of ≥5 drugs, excluding allopurinol or febuxostat

Why there is such a high prevalence of inappropriate prescription? Even though asymptomatic hyperuricemia affects 25–40 % of patients with untreated hypertension, a recent Cochrane review suggests that there is insufficient evidence to recommend the use of allopurinol or other hypouricemic drugs as an initial or adjuvant treatment of hypertension [11]. In addition, results of two large prospective genetic cohort studies found no evidence for causal associations between uric acid levels and ischemic heart disease or high blood pressure [12]. Our findings of a high prescription rate contrast with the established knowledge that allopurinol has a potential for rare but life-threatening skin and systemic side effects. The risk of severe cutaneous adverse reactions is estimated to be 10 times higher in allopurinol users than in non-users: about 2 % of treated patients develop a skin rash. Furthermore, mortality from the severe hypersensitivity syndrome is not trivial, 0.2/1000 patients dying every year following a severe adverse reaction to allopurinol [13, 14]. The risk of fatal allopurinol hypersensitivity syndrome occurs more often after inappropriate treatment of asymptomatic hyperuricemia, especially in the first 6 months of treatment [7, 13]. A recent report from the center of pharmacovigilance of the Lombardy Region (Italy) showed that among 10 cases of adverse reactions to allopurinol reported over a period of 12 months, 7 had severe skin reactions, including the Stevens-Johnson syndrome and one patients died: in all cases allopurinol therapy was not consistent with the current guidelines for the treatment of asymptomatic hyperuricemia and gout [15]. Furthermore, a case of rhabdomyolysis following the administration of febuxostat for hyperuricemia has been reported in a patient with chronic kidney disease [16].

Table 3 Association between XO inhibitors and adverse clinical outcomes at 3 months follow-up

Univariate analysis		
	OR (95 % CI)	*p* value
Adverse clinical events	1.68 (1.10–2.58)	0.02
Re-admission	0.84 (0.57–1.23)	0.36
All-cause mortality	1.30 (0.80–2.12)	0.30
Multivariate analysis[a]		
Adverse clinical events	1.74 (1.09–2.70)	0.02
Re-admission	0.73 (0.48–1.08)	0.12
All-cause mortality	1.22 (0.71–2.03)	0.46

[a] Adjusted for age, sex, hyperuricemia, hypertension, diabetes, ischemic cardiomyopathy, heart failure, and cardiac dysrhythmias

With this background, why allopurinol is so frequently prescribed? Assuming that prescription in asymptomatic hyperuricemic patients is meant to prevent an attack of gout, it must be considered that while the prevalence of hyperuricemia is about 5–8 % in adult white males in the USA, only 5 % of them will eventually develop gout [17]. It has been suggested that allopurinol could be of benefit for primary prevention in hypertensive and diabetic patients, especially those with left ventricular hypertrophy, and for secondary prevention in acute and chronic CVD. On the whole, available data indicate that the frequent choice to prescribe allopurinol to reduce various CVD in at risk populations is not supported by evidence, and must be balanced against rare but dangerous side effects. Indeed, no prospective randomized clinical trials

have shown cardiovascular benefits on relevant clinical outcomes in the frame of primary or secondary prevention. This notwithstanding, we found in REPOSI a strict association between diagnosis of CVD and allopurinol prescription at hospital discharge, and although we cannot establish with certainty a causal relationship between a diagnosis of CVD and allopurinol prescription, our study suggests a high rate of inappropriate prescription of XO inhibitors for unlicensed indications. Unfortunately, at the 3-month follow-up, inappropriately treated patients had a higher risk for adverse events then those appropriately not treated and no benefits were found with respect to the risk of re-hospitalization and mortality. These results were consistent after adjusting for clinical conditions where a benefit for allopurinol has been suggested but not established (hyperuricemia, hypertension, diabetes, ischemic, heart failure, and cardiac dysrhythmias) and although patients receiving allopurinol were being on long-term treatment.

Our study has limitations: the REPOSI registry was not set up to specifically investigate the appropriate use of XO inhibitors but more generally to collect information on elderly hospital patients with multimorbidities receiving multiple drugs. Lack of data about uric acid levels made impossible to evaluate the use of allopurinol in those few patients with asymptomatic hyperuricemia who may have had a benefit, such as those with persistently high uric acid levels (above 13 mg/dL in men or 10 mg/dL in women) with the associated nephrotoxic effect [18]; or in the presence of urinary excretion of uric acid exceeding 1100 mg daily, which has been associated with a 50 % increase in the risk of developing uric acid stones [19, 20]. Although this limitation tends to overestimate the rate of inappropriate prescription of XO inhibitors, it appears that for the majority of patients with asymptomatic hyperuricemia treatment with allopurinol is not justified by current evidences [15, 21]. Study limitations also include the relatively smaller number of patients with 3-month follow-up data, not available for about 25 % of those recruited. Moreover, no information was available on medication adherence, because we could not asses if a drug prescribed at hospital discharge was really taken. Lack of data on adverse clinical events and causes of death after discharge did limit the possibility of checking the association between XO inhibitors and adverse events, tending to underestimate the real risk.

Conclusions

The high prevalence of inappropriate prescription of XO inhibitors remained almost the same at admission and discharge. Inappropriate use of these drugs is principally related to treatment of asymptomatic hyperuricemia in patients with CVD, although no prospective randomized clinical trials have shown cardiovascular benefits. Stricter adherence to evidence-based guidelines is essential for a rational use of these drugs.

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Conflict of interest The authors have no conflict of interest.

Appendix

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