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ORIGINAL ARTICLE

Prescribing patterns of allopurinol and febuxostat according to directives on the reimbursement criteria and clinical guidelines: analysis of a primary care database

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ABSTRACT

Objective: According to American clinical guidelines, allopurinol and febuxostat may be prescribed as first-line therapy to treat hyperuricemia. However, the Italian Medicines Agency directive, called Nota 91, allows the reimbursement of second-line febuxostat in the case of failure and/or intolerance of a previous allopurinol therapy, so partially embracing European League Against Rheumatism recommendations and the British Society for Rheumatology Guideline. Such inconsistency might lead to heterogeneity among General Practitioners (GPs) in treatment of hyperuricemia. This study, therefore, aimed to evaluate the prescribing behavior of GPs in terms of compliance with Nota 91 and/or official guidelines.

Methods: Using the Health Search Database, a retrospective cohort study was conducted to evaluate the patterns of use of allopurinol and febuxostat between 2011 and 2016.

Results: In total, 44,257 and 5837 patients were prescribed with allopurinol and febuxostat, respectively. Among febuxostat users, 4321 (74%) had a previous allopurinol treatment; 92% of switches to febuxostat were related to hyperuricemia, whereas 9% of switchers presented intolerance to allopurinol; 26% of patients were prescribed with febuxostat as first-line therapy. The presence of diabetes and/or moderate/severe renal disease were statistically significant determinants of febuxostat use as first-line therapy.

Conclusion: Prescriptions of febuxostat were highly compliant to Nota 91. Only a sub-group of front-line prescriptions of febuxostat were mainly driven by the presence of renal dysfunction, which is able to increase the risk of allopurinol intolerance and/or inefficacy. These findings indicate that GPs' prescribing behavior for hyperuricemia is highly compliant with both regulatory directives and clinical guidelines.

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Introduction

Gout is one of the most common causes of inflammatory arthritis, with relevant reductions in quality-of-life. It is featured by deposition of monosodium urate (MSU) crystals within joints and surrounding tissues, as a consequence of long standing high blood urate levels[1,2]. Hyperuricemia is defined as serum uric acid (sUA) greater than 404 mmol/l (6.8 mg/dl), and can be caused by an increased metabolic production or a reduced renal excretion of urate[3]. Hyperuricemia is an essential but not sufficient condition for gout occurrence. Indeed, in a longitudinal study, only 22% of subjects with hyperuricemia (sUA> 9.0 mg/dl) developed gout during 5 years of study[4].

In North America and Western Europe the gout prevalence was estimated between 1–4%[5]. In Italy the prevalence was estimated ~0.9%[6]. The determinants for gout occurrence include age and sex (i.e. the risk increases after 65 years old and after menopause for men and women, respectively), comorbidities (e.g. metabolic syndrome, cardiovascular disease, and renal disease), dietary habits (e.g. purine-rich diet and alcoholic beverages increases the risk of gout), the use of certain pharmacological treatments (e.g. diuretics, anti-hypertensive drugs, ciclosporin, and low-dose aspirin) and, although rare, genetic variations. In this respect, function of urate transporters GLUT9, NPT1, URAT1, and OAT4 are affected by mutations of genes such as SLC22A12, SLC2A9, and ABCG2[1,7,8].

The use of urate-lowering therapy (ULT), nominally xanthine oxidase inhibitors and uricosuric medications (alone and/or in combination), is the mainstay pharmacotherapy to reduce the sUA[9–11]. The most prescribed ULTs is allopurinol, that has a purine-like structure and is effective in both

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under-excretion and over-production states. In 2011, a febuxostat non-purine selective inhibitor of both the oxidized and reduced forms of xanthine oxidase was launched[10–12].

European League Against Rheumatism (EULAR)[9] guidelines and the British Society for Rheumatology Guideline (BSR)[2] recommend allopurinol as first-line ULT to treat the major clinical manifestations associated with chronic deposition of uric acid/urate crystals in joints, or subcutaneous tissue (tophi). Febuxostat can be used in the case of failure of a previous therapy with allopurinol, defined as a new onset of acute gout attacks and/or hyperuricemia, or in patients with contraindications or intolerances to allopurinol (i.e. anaphylaxis, serious cutaneous adverse reactions, liver failure, and chronic kidney disease). Instead, the American College of Rheumatology (ACR) advises either allopurinol or febuxostat as first-line therapy[10].

In Italy, the reimbursement criteria of febuxostat are regulated by the Italian Medicines Agency directive called Nota 91, that is partially based on EULAR and BSR guidelines limiting the use of febuxostat as second-line therapy[2,9,13]. This partial heterogeneity among Nota 91, EULAR, BSR guidelines, and ACR recommendations could, therefore, lead to different prescribing behaviors among Italian general practitioners (GPs).

To date, few studies have evaluated the patterns of prescriptions for allopurinol and febuxostat in primary care. This study aims to evaluate the compliance to Nota 91 and/or clinical guidelines with regard to allopurinol and febuxostat prescription, and to characterize clinical features influencing the therapeutic choice between these two medications.

Methods

Data source

We adopted the Health Search Database (HSD), a longitudinal observational database established in 1998 by the Italian College of General Practitioners and Primary Care, containing the electronic patient records from ~1000 GPs homogeneously distributed across Italy. Computer-based patient records collected by a selected group of 800 GPs, who met standard quality criteria regarding the levels of data entry (i.e. levels of coding, prevalence of selected diseases, rates of mortality, and years of recording), were included in the present study[14]. These GPs covered almost 1 million patients, and were geographically distributed to include patients' representative of the whole Italian population, and to ensure the completeness and consistency of medical records[15,16].

Records consisted of demographic details; medical information, such as diagnoses, drugs, and diagnostic test prescriptions; specialist referrals; lifestyle characteristics and mortality. These data were linked through a unique anonymous identification code.

All diagnoses were coded according to the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM). To complement the coded diagnoses, GPs are enabled to add free text.

Information on drug prescriptions includes the name of the prescribed drug (i.e. active substance and/or brand name), the corresponding Anatomical Therapeutic Chemical (ATC) code, along with the related defined daily dose (DDD), the date of prescription, and number of days' supply. The ATC/DDD is a validated classification system from the World Health Organization (WHO), considered the standard reference for coding medications in several countries[17]. Every prescription is associated with specific diagnoses (i.e. indication of use). A number of epidemiological studies have been conducted using HSD aligned to the European Union guidelines on the use of medical data for research[6,18,19].

Study population

We selected patients aged ≥18 years being prescribed with allopurinol (ATC codes: M04AA01, M04AA51) or febuxostat (ATC code: M04AA03) between January 1, 2011 (year of febuxostat launch) and December 31, 2016. The date of this prescription was the study index date. We excluded patients with less than 1 year of recorded medical history prior to the index date.

Outcome measures

We evaluated whether febuxostat prescriptions were compliant with Nota 91 through the following criteria: (i) prescriptions of febuxostat as second-line therapy in the case of therapeutic failure of allopurinol; and (ii) prescription of febuxostat as second-line therapy in the case of intolerance and/or contraindications to allopurinol.

Operationally, therapeutic failure of allopurinol was defined on these criteria: presence of gout flares following the prescription of allopurinol and preceding the prescription of febuxostat on the bases of: (1) specific ICD-9-CM codes for gout diagnosis (274.0: gouty arthritis; 274.1: gouty nephropathy; 274.8: gout with other unspecified manifestations; 274.9: gout) coupled with prescription of colchicine (ATC code M04AC01), non-steroidal anti-inflammatory drugs (NSAIDs) (ATC codes M01A*) or systemic corticosteroids (ATC codes H02*). To distinguish between the use of these medications for gout flares and their concurrent use with allopurinol initiation, we applied a latency period of 90 days following allopurinol prescription; (2) registration of ICD-9-CM coding calculus of kidney and ureter (592*, 594.1) or renal colic (788.0), and/or the presence of 'tophi' verbatim in the free-text files (3 months before or after a gout diagnosis); (3) presence of sUA levels higher than 6 mg/dl (360 mmol/l) or registration of ICD-9-CM code 274.9 combined with the clinical term 'hyperuricemia'. To quantify sUA levels, we collected any laboratory test value recorded in the period between the prescription of allopurinol and febuxostat. Thus, we conducted two calculations: the mean between (a) the last value of sUA registered in HSD before the febuxostat prescription and (b) the mean value of all sUA values registered in the previous 90 days.

Operationally, we identified patients with intolerance and/or contraindications to allopurinol according to these

criteria. Presence of (1) anaphylaxis (ICD-9-CM: 995.0, 995.2, 995.3, 995.6, 999.4, 999.8 or related keywords in free-text files); (2) serious cutaneous reactions (ICD-9-CM: 695.1 or related keywords in free-text files); (3) rash and other non-specific skin eruptions (ICD-9-CM: 782.1); (4) generalized vasculitis (ICD-9-CM: 136.1, 273.2, 287.0, 362.18, 437.4, 443.1,446, 447.6, 448.9); (5) seizures (ICD-9-CM: 344.89, 345, 779.0, 780.3); (6) abnormal liver function tests (alanine aminotransferase, ALT >40 UI/l; aspartate aminotransferase, AST >35 UI/l; alkaline phosphatase, AP >140 UI/l); (7) liver injury (ICD-9-CM: 570*, 573.3*, 794.8*, 572.2*); (8) chronic renal failure (CRF)/renal disease (ICD-9-CM: 585, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93; 250.4, 581.1, 581.8, 583.81, 791.0) whenever they were registered within 90 days following every prescription of allopurinol.

The determinants on the prescription choice regarding allopurinol and/or febuxostat have been investigated in the period preceding or on the index date. They included ischemic stroke, transient ischemic attack, hemiparesis, or intracerebral hemorrhage (ICD-9-CM: 342*, 430, 431, 432*–436*, 438*); coronary artery disease (ICD-9-CM: 410*–414*); diabetes (ICD-9-CM: 250*); hypertension (ICD-9-CM: 401*–405*, or the last systolic and diastolic pressure levels recorded during 90 days before and on the index date, greater than 140 or 85 mmHg, respectively); lipid disorders (ICD-9-CM: 272* or cholesterol levels higher than 200 mg/dl, serum low-density lipoprotein (LDL) higher than 100 mg/dl considering the last value recorded during 90 days before and on the index date, serum high-density lipoprotein (HDL) lower than 40 mg/dl for men and 46 mg/dl for women, and levels of triglycerides higher than 150 mg/dl considering the mean values recorded during 12 months before or on the index date); hyperuricemia considering the last available value of uric acid >360 mg/dL, recorded during 90 days before and on the index date or the ICD-9-CM 274* combined with the term 'hyperuricem*'.

Chronic kidney disease was defined by the corresponding ICD-9-CM codes (585, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93; 250.4, 581.1, 581.8, 583.81, 791.0) whose severity was categorized into mild (glomerular filtration rate, GFR ≥60 ml/min/1.73 m^2), moderate (GFR = 30–59 mL/min/1.73 m^2), and severe (GFR = 15–29 mL/min/1.73 m^2).

Data analyses

The degree of compliance to Nota 91 among patients prescribed with febuxostat was quantified according to descriptive statistics. Namely, continuous variables were reported as mean values (standard deviation (SD)) and categorical variables as *n* and percentages.

Multivariate logistic regressions were used to estimate the determinants of treatment choice between allopurinol and/or febuxostat. Odds ratios (ORs) and related 95% confidence intervals (CI) were used as measures of association. The analyses were stratified according to previous use of allopurinol.

Table 1. Evaluation of compliance to Nota 91 among patients treated with febuxostat and previously prescribed with allopurinol.

	Patients treated with febuxostat and with a previous prescription of allopurinol ($n = 4321$)
Compliance with Nota 91 for at least one criteria	
Yes	4040 (93.5)
No	281 (6.5)
Number of acute attacks of gout	
0	3776 (87.4)
1	368 (8.52)
2	88 (2)
3	29 (0.7)
≥ 4	60 (1.39)
High sUA level	
Hyperuricemia (mean laboratory values)	
Yes	3994 (92.4)
No	327 (7.6)
Intolerance or contraindication to allopurinol	
Yes	398 (9.2)
No	3923 (90.8)

Abbreviation: sUA, serum uric acid.

All statistical analyses were performed using the software STATA, version 13. To assess the robustness of results, we performed a sensitive analysis.

In keeping with some guidelines, the ULT therapy should be continued for 90–180 days to prevent gout flares[2,9,11]. We, therefore, repeated the analysis using a different definition of gout flares, by extending the latency period to 18 days after allopurinol prescription.

Results

The study population included 44,257 patients with a prescription of allopurinol and 5837 patients with a prescription of febuxostat. Among febuxostat users, 4321 (74%) reported prior use of allopurinol, and were, therefore, considered for the assessment of compliance to Nota 91 (Table 1). Of them, 4040 patients (93.5%) had prescriptions compliant with the Nota 91 for at least one criteria. Specifically, hyperuricemia resulted in being the main criteria for compliance; in particular, 3994 (92.4%) patients reported high sUA considering the mean laboratory value of sUA. Only 545 patients (12.6%) presented acute gouty attacks, and 398 (9.2%) had experienced intolerance and/or contraindications to allopurinol. In the sensitivity analysis which adopted a 180 days latency period after allopurinol prescription, the results were comparable to those obtained with the primary analysis.

Table 2 reports the demographic and clinical features of febuxostat users stratified according to the presence or absence of previous allopurinol therapy. Patients using febuxostat as second-line therapy, i.e. in compliance with Nota 91, were mainly males (OR = 1.31; 95% CI = 1.23–1.40) and were more frequently affected by comorbidities such as coronary artery disease (OR = 1.15; 95% CI = 1.07–1.24), diabetes mellitus (OR = 1.11; 95% CI = 1.04–1.19), hypertension (OR = 1.43; 95% CI = 1.31–1.57), dyslipidemia (OR = 1.18, 95% CI = 1.1–1.26), and hyperuricemia (OR = 1.59; 95% CI = 1.47–1.43). In addition, these patients were characterized by impaired renal function,

Table 2. Demographic and clinical features of patients treated with febuxostat according to a previous exposure to allopurinol.

		Previous treatment with allopurinol			No previous treatment with allopurinol		
	Allopurinol ($n = 44,257$) *n* (%)	Febuxostat ($n = 4321$) *n* (%)	OR (95% CI) (unadjusted)	OR (95% CI) (adjusted)	Febuxostat ($n = 1516$) *n* (%)	OR (95% CI) (unadjusted)	OR (95% CI) (adjusted)
Age							
Mean ± SD	70.6 (13.5)	73.4 (11.6)	1.02 (1.01–1.02)	1.01 (1.01–1.01)	72.2 (13.2)	1.01 (1.01–1.01)	1.00 (1–1.009)
Sex							
Female	18,211 (41.1)	1668 (38.6)	Ref.	Ref.	648 (42.7)	Ref.	Ref.
Male	26,046 (58.9)	2653 (61.4)	1.11 (1.05–1.18)	1.31 (1.23–1.4)	868 (57.3)	0.94 (0.84–1.04)	1.00 (0.9–1.12)
Co-morbidity							
Ischemic stroke/ transient ischemic attack	5,537 (12.5)	629 (14.6)	1.19 (1.09–1.3)	0.94 (0.86–1.02)	212 (14)	1.14 (0.98–1.32)	1.01 (0.87–1.18)
Coronary artery disease	7,628 (17.2)	971 (22.5)	1.39 (1.3–1.49)	1.15 (1.07–1.24)	313 (20.6)	1.25 (1.1–1.42)	1.1 (0.97–1.26)
Diabetes mellitus	11,898 (26.9)	1408 (32.6)	1.31 (1.23–1.4)	1.11 (1.04–1.19)	489 (32.3)	1.29 (1.16–1.44)	1.2 (1.08–1.35)
Hypertension	34,486 (77.9)	3731 (86. 3)	1.79 (1.64–1.95)	1.43 (1.31–1.57)	1218 (80.3)	1.16 (1.02–1.32)	1.06 (0.92–1.21)
Dyslipidemia	27,341 (61.8)	2942 (68. 1)	1.32 (1.24–1.41)	1.18 (1.1–1.26)	880 (58)	0.86 (0.77–0.95)	0.9 (0.81–1.01)
Hyperuricemia (diagnosis or mean laboratory values)	31,603 (71.4)	3494 (80.9)	1.69 (1.57–1.82)	1.59 (1.47–1.73)	986 (65)	0.74 (0.67–0.83)	0.76 (0.68–0.86)
Renal function							
Normal	38,183 (86.3)	3009 (69.6)	Ref.	Ref.	1158 (76.4)	Ref.	Ref.
Mild reduction in GFR	554 (1.3)	72 (1.7)	1.65 (1.31–2.08)	1.38 (1.09–1.74)	18 (1.2)	1.07 (0.67–1.72)	1.1 (0.68–1.76)
Moderate reduction in GFR	2,430 (5.5)	529 (12.2)	2.76 (2.52–3.02)	2.27 (2.07–2.49)	138 (9.1)	1.87 (1.57–2.24)	1.87 (1.56–2.26)
Severe reduction in GFR	882 (2)	284 (6.6)	4.09 (3.63–4.6)	3.53 (3.12–3.99)	66 (4.4)	2.47 (1.91–3.18)	2.36 (1.82–3.06)
Missing	2,048 (4.6)	—	—	—	—	—	—

Abbreviations: CI, confidence interval; GFR: glomerular filtration rate; SD, standard deviation.

namely a moderate (OR = 2.27, 95% CI = 2.07–2.49) and severe reduction in GFR (OR = 3.53, 95% CI = 3.12–3.99).

When we investigated the use of febuxostat ($n = 1516$) vs allopurinol ($n = 44,257$) as first-line therapy, the results showed that hyperuricemia was associated with higher use of allopurinol (OR = 0.76, 95% CI = 0.68–0.86), while cardiovascular and cerebrovascular diseases did not raise any preferred choice between allopurinol or febuxostat. In contrast, the first-line prescription of febuxostat was significantly higher in patients with diabetes mellitus (OR = 1.20, 95% CI = 1.08–1.35) and with moderate (OR = 1.87, 95% CI = 1.56–2.26) and severe reduction in GFR (OR = 2.36, 95% CI = 1.82–3.06).

Discussion

This study investigated the patterns of use of allopurinol and febuxostat in the setting of Italian primary care. Our findings indicate a prominent prescription of allopurinol as first line-therapy. Among 5837 patients prescribed with febuxostat, 26% of them were exposed to first-line treatment. Most febuxostat prescriptions were compliant with Nota 91, while the prescription of febuxostat as first-line therapy was mainly driven by the clinical condition of patients, in particular the reduced renal function, in line with clinical guidelines.

In 74% of cases, febuxostat was preceded by a treatment with allopurinol: use of allopurinol as first-line treatment is recommended by current EULAR and BSR guidelines and by the Italian Medicines Agency (Nota 91), with switch to febuxostat being indicated in the case of poor control of sUA levels, intolerance, and/or contraindications related to therapy with allopurinol[2,9,13]. In line with these recommendations, we found that hyperuricemia was the most frequent cause for treatment switch from allopurinol to febuxostat. Reducing sUA levels is a key treatment goal, since it prevents acute attacks and long-term complications such as tophi, joint destruction, nephrolithiasis, gout nephropathy, and renal failure[20].

In our study, more than 10% of patients switching to febuxostat had experienced at least one acute gout attack during previous allopurinol treatment. Adherence to ULT is, therefore, a key issue in the management of gout. According to a study by Mantarro *et al.*[21] conducted in this same setting, only 3.2% of patients were adherent to allopurinol over 1-year follow-up. Poor adherence to allopurinol seems mainly related to its tolerability profile[22], given that allopurinol causes adverse reactions in 2–8% of users[23–26]. According to a case-control study conducted on patients prescribed with allopurinol for either symptomatic gout, asymptomatic hyperuricemia, or tumor lysis syndrome, 5% of patients experienced adverse events, after a mean time of 6 weeks since treatment initiation[27]. Most common adverse reactions included skin rash, gastrointestinal events, neurologic events, fever, musculoskeletal events, and allopurinol hypersensitivity syndrome (AHS). Of note, AHS causes death in up to 27% of cases[23–26]. Risk of severe adverse events, including AHS, such as Stevens–Johnson syndrome and toxic epidermal necrolysis, is known to increase in renal disease[28,29]. In our study, ∼ 9% of cases of switch from allopurinol to febuxostat were related to intolerance or contraindication to previous allopurinol treatment.

According to multivariate analysis, we found that the presence of renal failure was significantly more common in

patients that switched from allopurinol to febuxostat compared to those staying on allopurinol. Furthermore, we found that switchers had significantly higher proportions of cardiovascular comorbidities, such as coronary artery disease, diabetes, hypertension, and dyslipidemia. Correlation of uncontrolled hyperuricemia and increased risk of both cardiovascular and renal diseases is well known in the literature[9,30,31]. In this context, as shown by White *et al*.[32], there is still contrasting evidence supporting a similar cardiovascular risk profile for allopurinol and febuxostat among cardiovascular disease sufferers.

As previously reported, the majority of patients in our setting were treated with febuxostat as second-line treatment, i.e. in accordance with EULAR, BSR, and Italian Medicines Agency recommendations (Nota 91). However, we found that 26% of patients were prescribed with febuxostat as first-line therapy, without previous prescriptions of allopurinol. These prescriptions might be seen as not adherent to the Nota 91, so they are not allowed to be reimbursed by the public health system. According to multivariate analysis, we found that only diabetes mellitus and moderate/severe renal failure remained statistically significant determinants for the first-line prescription of febuxostat vs allopurinol, even if the related point estimates showed a lower effect size than those estimated for second-line use of febuxostat. Renal failure can indeed prevent allopurinol dose escalation sufficient to achieve the therapeutic target, and is also associated with increased risk of adverse events as described in EULAR, BSR guidelines, and ACR recommendations[2,9,10,28,29]. However, this clinical condition and its implication on adverse events is not mentioned in Nota 91[13], and the best urate-lowering treatment in gout patients with impaired renal function is still debated. Indeed, a recent publication by Stamp *et al*.[33] showed that dose escalation of allopurinol according to creatinine clearance is a reliable strategy to lower sUA.

Thus, GPs' prescriptions of febuxostat as first-line treatment might have been driven by this clinical evidence, as described in clinical guidelines, even if these prescriptions are not allowed to be reimbursed by the National Health System[2,9,10].

This study has some limitations. First, as the prescription records only reflect what was prescribed and not what was actually consumed. However, we attempt to investigate GPs' prescribing behavior, which was not biased by this shortcoming, and the presence of switching or stay on therapy for allopurinol are indicators of actual use. Furthermore, sUA values of some laboratory tests might have been missing. Nevertheless, the epidemiology of gout and hyperuricemia has been previously demonstrated in HSD[6], and these same operational definitions have been adopted in our study.

Conclusion

This study provides relevant information about patterns of use of allopurinol and febuxostat in the setting of Italian general practice. Our findings show that prescriptions of febuxostat are highly compliant to Nota 91, so confirming a preferred choice of allopurinol as first-line therapy.

Prescriptions of febuxostat as first-line therapy, outside recommendations of Nota 91, were mainly related to the presence of diabetes and/or impaired renal function. The latter is a condition that is well described in clinical guidelines and is associated with increased risk of both allopurinol intolerance and inefficacy. Along this line, diabetes is a well-known predictor for renal complications. This finding could, therefore, explain the use of first-line febuxostat out of Nota 91. Despite new evidence, the prescribing behavior of the Italian GPs is, therefore, highly compliant with regulatory directives and official guideline, but prescriptions of first-line febuxostat are not allowed to be reimbursed by the National Health System.

Transparency

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Declaration of financial/other interests

F. Lapi has provided consultancies in protocol preparation for epidemiological studies and data analyses for Menarini, IBSA and Angelini. C. Cricelli provided clinical consultancies for Menarini, IBSA, Angelini, Grunenthal, Alfa Wasserman, Pfizer, Prostrakan, Molteni, Dompè, and Teva. G. Medea E. provided clinical consultancies for Menarini, IBSA, Angelini, Alfa Wasserman, and Bayer. CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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