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Original article

Risk of cutaneous adverse events with febuxostat treatment in patients with skin reaction to allopurinol. A retrospective, hospital-based study of 101 patients with consecutive allopurinol and febuxostat treatment

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ABSTRACT

Objective: To investigate the cutaneous tolerance of febuxostat in gouty patients with skin intolerance to allopurinol.
Methods: We identified all gouty patients who had sequentially received allopurinol and febuxostat in the rheumatology departments of 4 university hospitals in France and collected data from hospital files using a predefined protocol. Patients who had not visited the prescribing physician during at least 2 months after febuxostat prescription were excluded. The odds ratio (OR) for skin reaction to febuxostat in patients with a cutaneous reaction to allopurinol versus no reaction was calculated. For estimating the 95% confidence interval (95% CI), we used the usual Wald method and a bootstrap method.
Results: In total, 113 gouty patients had sequentially received allopurinol and febuxostat; 12 did not visit the prescribing physician after febuxostat prescription and were excluded. Among 101 patients (86 males, mean age 61 ± 13.9 years), 2/22 (9.1%) with a history of cutaneous reactions to allopurinol showed skin reactions to febuxostat. Two of 79 patients (2.5%) without a skin reaction to allopurinol showed skin intolerance to febuxostat. The ORs were not statistically significant with the usual Wald method (3.85 [95% CI 0.51–29.04]) or bootstrap method (3.86 [95% CI 0.80–18.74]).
Conclusion: The risk of skin reaction with febuxostat seems moderately increased in patients with a history of cutaneous adverse events with allopurinol. This moderate increase does not support the cross-reactivity of the two drugs.

1. Introduction

Lowering serum urate level to <6 mg/dL is a major goal of gout management, allowing for dissolution of the pathogenic monosodium urate crystals, disappearance of gout features and prevention of the detrimental course of the disease [1,2]. Allopurinol is a urate-oxydase inhibitor that has been used for several decades for managing hyperuricemia and is still the leading hypouricemic drug. Its efficacy is dose-related, and doses greater than the most frequently prescribed 300 mg/d are often required to reach the uricemia target [3]. The main side effects of allopurinol are cutaneous and occur mainly within the 3 months after treatment initiation or dose increase.

Serious cutaneous adverse reactions (SCARs) are rare but life-threatening side effects of allopurinol. They include toxic epidermal necrosis, Stevens–Johnson syndrome, drug rash with eosinophilia

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and systemic symptoms (DRESS), vasculitis, and multisystem allopurinol hypersensitivity syndrome [4]. A propensity score – matched cohort study comparing allopurinol initiators and non-allopurinol users found a crude incidence rate of SCARs in patients receiving allopurinol of 0.69 (95% confidence interval [95% CI] 0.50–0.92) per 1000 person-years [5]. Allopurinol has been estimated to cause about 44 cases (14 fatal) of Stevens–Johnson syndrome for every million newly treated patients [5]. In the EuroSCAR case-control study, allopurinol accounted for 5% of cases of SCARs [6]. The SCAR incidence can be decreased by allopurinol titration [7]. However, renal failure might increase the risk of SCARs, so most European regulatory agencies have limited allopurinol dosing according to creatinine clearance [8]. Mild skin rashes are reported in 2% to 4% of patients receiving allopurinol [9–11]. Even if rashes resolve after allopurinol cessation, they are considered life-long contraindications to the reintroduction of allopurinol because of increased risk of SCARs.

Alternatives to allopurinol in intolerant patients include febuxostat, a recent, non-purine xanthine oxidase inhibitor that is structurally distinct from allopurinol [12–14]. However, febuxostat can also lead to cutaneous side effects, the frequency of which was estimated at 5.2% (95% CI 2.1–10.5%) in the phase III studies of the registration dossier [15] Moreover, a few case reports of SCARs with febuxostat were potentially associated with a history of skin reaction to allopurinol, particularly in patients with renal failure [16,17]. Post-marketing surveillance data led the French agency to inform prescribers about a potential cross-reactivity between allopurinol and febuxostat [18], which is important to consider when an alternative to allopurinol is needed for managing gout.

We conducted a retrospective cohort study of all patients consecutively receiving allopurinol and febuxostat in 4 hospitals in France to assess the risk of skin reaction to febuxostat in patients with prior cutaneous reactions to allopurinol.

2. Methods

We retrospectively collected an exhaustive cohort of patients consecutively treated with allopurinol and febuxostat in real-life conditions. Rheumatology departments from 4 university hospitals in France with recognized experience in treating gout (Lariboisière, Paris; Salengro and Saint Philibert hospitals, Lille; Hospital-Sud, Rennes) participated. We included all patients fulfilling the American Rheumatology Association preliminary criteria for the classification of gout [19], who had consecutively received allopurinol and febuxostat for at least 2 months or had prematurely discontinued either of the drugs because of a skin reaction. The time interval between receipt of the two drugs and whether treatment with one of the drugs was still ongoing did not affect inclusion. Patients were identified from the date of introduction of febuxostat in France (April 2009) until February 2014. Patient records were analyzed by physicians belonging to the hospital centers who used a pre-established questionnaire. Collected data included demographics, history of skin reaction to allopurinol or febuxostat, whether the reaction had led to drug discontinuation, and history of skin reaction to other drugs if available. Blood creatinine and urate levels at the start of febuxostat were collected if available.

2.1. Statistical analysis

Data are expressed as mean ± SD for continuous variables and number (%) for categorical variables. Dyslipemia was defined as hypercholesterolemia (total cholesterol level > 2 g/L) or hypertriglyceridemia (blood triglyceride level > 1.5 g/L) and/or receiving lipid-lowering treatment. Renal function was as mentioned by the physician in charge. Patients were cross-classified in terms of history of allopurinol skin reactions and history of febuxostat skin reactions. Odds ratios (ORs) were calculated in a logistic regression model and were expressed with two-sided 95% confidence intervals calculated with the Wald method (95% CIs). Increased risk of febuxostat skin reaction in patients with allopurinol skin reaction was defined as a lower bound of 95% CI > 1. Because our population was small and we expected a large 95% CI, we used bootstrapping, a data-base simulation method for assigning measures of accuracy to statistical estimates [20]. The bootstrap simulates what would happen if repeated samples of the population could be analyzed by taking repeated samples of the data available. We created 5000 random replicates of our population by random selection with replacement and calculated the OR in each replicate, thereby obtaining 5000 ORs with a logarithmic distribution. We calculated the mean and 2.5th and 97.5th percentiles of the log-transformed ORs (namely the 125th and the 4875th values) and expressed the results by their antilog. Statistical analyses involved use of SAS 9.3. (SAS Inst., Cary, NC, USA).

Table 1
Features of the 101 patients included in the study.

	n[a]	
Men	101	86 (85%)
Age (years), mean ± SD [median; range]	96	61.5 ± 13.9 [62.1; 25.5–86.6]
Hypertension	89	62 (69.7%)
Obesity	86	30 (34.9%)
Type II diabetes	84	26 (31.0%)
Dyslipemia	80	50 (62.5%)
Renal failure	90	41 (45.6%)
Uric lithiasis	74	7 (9.5%)
Duration of gout (years), mean ± SD [median; range]	82	16.89 ± 13.52 [14; 0–55]
Tophi	84	59 (70.2%)
Age at initiation of febuxostat (years), mean ± SD; [median; range]	95	58.81 ± 13.93 [60; 24–85]
Creatinine level at initiation of febuxostat (μmol/L), mean ± SD; [median; range]	47	81.47 ± 79.06 [80; 6–296]

Obesity: BMI (body mass index) > 30 kg/m^2; dyslipemia: hypercholesterolemia (total cholesterol > 2 g/L)or hypertriglyceridemia (blood triglycerides > 1.5 g/L) or ongoing lipid-lowering treatment; results are expressed as mean ± standard deviation [minimum–maximum; median].

[a] Patients with information.

3. Results

3.1. Population

We examined hospital files for 554 gouty patients (Lariboisière, n = 291; Salengro, n = 116, Saint Philibert, n = 51; Hôpital-Sud, n = 96); 372 had received allopurinol, 159 had received febuxostat and 113 had consecutively received allopurinol and febuxostat. Among these patients, 12 did not visit the prescribing physician after the initiation of febuxostat and were excluded from the analysis. Among the 101 included patients (86 males, mean age 61 ± 13.9 years), hypertension, type II diabetes and dyslipidemia were frequently associated with gout (Table 1). In all, 41/90 patients with available data had renal failure, as stated by the physician in charge, at the time they started febuxostat treatment. Files for 5 patients mentioned a history of allergy to another treatment.

3.2. Skin reactions

Overall, 22 patients (21.8%) experienced cutaneous adverse events with allopurinol (Table 2). Skin reactions were mild in 16 (pruritus, exanthema, eczema, fixed pigmented erythema) and