

Cutaneous adverse events with febuxostat after previous reactions to allopurinol: comment on the article by Singh and Cleveland

Dear Editor,

We read with interest the recent article by Singh and Cleveland on the hypersensitivity risk of allopurinol (ALP) and febuxostat (FBX) compared with colchicine.¹ A common challenge when using ALP, linked to hypersensitivity reactions, is the potential development of cutaneous adverse reactions (CARs). Most are often mild, non-specific rashes; however, severe CARs, including Stevens-Johnson syndrome (SJS), may occur, but with a low incidence (0.69 cases per 1000 person-years) in non-Asian populations.² In the EuroSCARs study, ALP was the reason for 5% of all severe CARs.³ So, FBX is often chosen as urate-lowering agent on the background of an ALP-related CAR. However, these patients were not eligible for the pivotal trials of FBX⁴ and were excluded from the recent analysis by Singh and Cleveland.¹ Therefore, the accurate rate of FBX-related CARs in patients who previously suffered from ALP, and the mechanisms behind, remain undetermined to date.

We have retrospectively reviewed patients with gout (diagnosed by crystals or American College of Rheumatology/European League Against Rheumatism criteria) treated with FBX after a previous CAR to ALP, from seven rheumatology units with members of the Crystal Arthritis Group of the Spanish Society of Rheumatology.

The study period spanned from 2011 (FBX commercialisation in Spain) to June 2018. Patients' records were reviewed for demographics, clinical features (type of skin events, ALP and FBX starting doses and doses at the time of rash), and serum urate levels and glomerular filtration rates at the time of prescription. Our primary study variable was the rate (%) of patients developing skin reactions with FBX. Descriptive analysis with an estimation of the 95% CI is given.

The study centres provided 67 patients with gout and a previous ALP-related CAR who were later treated with FBX (table 1). The median age was 71 years (p25-75 59.8–79.5), with 49 being male (73.1%). Most ALP cases were mild, but three developed SJS (table 1). Starting dosing was variable, and the percentage of chronic kidney disease was 58.0%.

Ten of these 67 patients (14.9%, 95% CI 8.3% to 25.3%) also developed rash with FBX, with the same proportion between male and female. Median (p25-75) time from ALP-rash to FBX initiation was 5.0 months (1.0–71.8). Numbers of serum urate levels and estimated glomerular filtration rates were similar in this subgroup. Types of rash were variable; to note, one patient with prior ALP-related SJS also developed with FBX.

Benzbromarone was successfully initiated in 19 patients (seven with CAR with both ALP and FBX), only one also developing a non-specific rash.

Our multicentre data identified around 15% of patients with prior ALP-related CARs also developed them with FBX. This rate is higher than previously reported. In an initial series of 13 patients with ALP-related CAR, only one developed it with FBX,⁵ while 9% of reactions with ALP and FBX in a study with 113 patients was published in 2016.⁶ Despite having the same target (the xanthine oxidase), FBX and ALP have no similarities on biochemical structure, so the identified cross-reaction is intriguing. The likelihood of developing ALP-related CARs

Table 1 Main clinical and laboratory data of the whole sample (patients developing allopurinol-related cutaneous adverse reactions) and of those who showed after switching to febuxostat

	Skin reaction with allopurinol (n=67)	Skin reaction with febuxostat (n=10)
Age, in years	71.0 (59.8–79.5)	65.0 (54.8–69.0)
Males, n (%)	49 (73.1%)	5 (50%)
Type of reaction, n (%)		
Non-specific	55 (82.1%)	8 (80%)
Maculopapular	9 (13.4%)	1 (10%)
SJS	3 (4.5%)	1 (10%)
Glomerular filtration rate, in mL/min	67.0 (44.9–89.3)	78.8 (42.8–90.6)
Serum urate, in mg/dL	8.4 (7.8–9.9)	8.1 (5.1–9.9)
Starting dose, in mg/day	100 (range 50–300)	80 (40–80)
Dose at time of CAR, in mg/day	300 (138–300)	10 (n=1), 40 (n=4), 80 (n=5)

Data shown as median (IQR), unless otherwise specified.

CAR, cutaneous adverse reaction; SJS, Stevens-Johnson syndrome.

mainly depends on starting dose and renal function.⁷ In Europe, FBX is only licensed as 80 and 120 mg tablets, while 40 and 80 mg are available in the USA. Whether using FBX at lower dosage might reduce the incidence of cross-reactions with ALP merits investigation, but to note, in our series, one patient also developed CAR with FBX dispensed at 10 mg.

Further prospective and intervention studies are needed to confirm these results, although caution is recommended when using FBX in this subgroup of patients.

Neus Quilis ¹, Paloma Vela,² Boris A Blanco Cáceres,³ Cesar Diaz-Torne ⁴, Enrique Calvo-Aranda,⁵ Francisca Sivera ^{6,7}, Alejandro Prada-Ojeda,⁸ Fernando Pérez Ruiz,³ Eliseo Pascual,⁹ Mariano Andrés¹⁰

¹Rheumatology Unit, Hospital Universitario del Vinalopo, Elche, Alicante, Spain

²Rheumatology Department, Hospital General Universitario de Alicante, Alicante, Spain

³Rheumatology, Hospital Universitario Cruces, Barakaldo, País Vasco, Spain

⁴Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

⁵Rheumatology, Hospital Universitario HM Sanchinarro, Madrid, Spain

⁶Medicine, Miguel Hernandez University of Elche Faculty of Medicine, Sant Joan D'Alacant, Spain

⁷Rheumatology, Hospital General Universitario Elda, Spain

⁸Rheumatology, Hospital Universitario de Torrejón, Torrejón de Ardoz, Madrid, Spain

⁹Rheumatology, Hospital General Universitario de Alicante, Alicante, Spain

¹⁰Rheumatology, Hospital de Alicante, Alicante, Spain

Correspondence to Dr Neus Quilis, Rheumatology Unit, Hospital Universitario del Vinalopo, 03010 Alicante, Spain; neqima87@hotmail.com

Twitter Cesar Diaz-Torne @cesardiaztorne, Enrique Calvo-Aranda @enriquecalvoA and Francisca Sivera @FranciscaSivera

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ORCID iDs

Neus Quilis <http://orcid.org/0000-0001-7509-7212>

Cesar Diaz-Torne <http://orcid.org/0000-0001-6275-7699>

Francisca Sivera <http://orcid.org/0000-0002-3414-1667>

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