Febuxostat Desensitization in a Patient with Previous Stevens-Johnson Syndrome and *HLA-B*58:01* Genotype

To the Editor:

We describe the first case, to our knowledge, of successful desensitization to febuxostat in a young high-risk patient of Filipino descent with *HLA-B*58:01* positive genotype and previous drug-induced Stevens-Johnson Syndrome (SJS), with 2 subsequent episodes of a morbilliform rash with repeat exposures to febuxostat.

Drug-induced severe cutaneous adverse reactions (SCAR) include a wide variety of different cutaneous manifestations including SJS, toxic epidermal necrolysis (TEN), drug-induced hypersensitivity syndrome, and drug reaction with eosinophilia and systemic signs (DRESS). Allopurinol, anticonvulsants, and antibiotics are among the most common causes, with allopurinol being the most common trigger. The mortality rate for allopurinol-induced SCAR is as high as 25% in certain genotypes and ethnicities[1]. The HLA-B*58:01 risk allele is strongly associated with SCAR, with variable prevalence rates in specific ethnicities; most notably in the Asian population[1]. However, in a metaanalysis of 9 population-control studies, HLA-B*58:01 for detecting allopurinol-induced TEN/SJS was found to be universal in Chinese, Japanese, and white populations[2].

The 2015 Clinical Pharmacogenetics Implementation Consortium guidelines[1] state that use of allopurinol is contraindicated in carriers of *HLA-B*58:01*. The 2012 American College of Rheumatology Guidelines for gout management recommend HLA-B*58:01 allele testing in selected subpopulations with elevated risk for allopurinol hypersensitivity syndrome (Korean descent with ≥ stage 3 kidney disease, Han-Chinese, or Thai descent)[3]. This recommendation was supported by a 2017 study that shows it is cost-effective to test for *HLA-B*58:01* prior to starting allopurinol in Asians, but not for whites or Hispanics[4]. As of August 2018, the US Food and Drug Administration has yet to make specific recommendations in its Pharmacogenomic Biomarkers in Drug Labeling Table[5].

Febuxostat is a second-line uric acid–lowering agent in patients with refractory gout. Febuxostat is structurally unrelated to allopurinol but it has also been reported to cause drug-induced SJS. The possibility of cross-reactivity due to inhibition of xanthine oxidase has been raised[6]. For the most part, patients allergic to allopurinol have been excluded from febuxostat clinical trials, and studies investigating the safety and efficacy of febuxostat and allopurinol have excluded *HLA-B*58:01*-positive patients with gout[7]. However, in a study of 13 patients with severe adverse reactions to allopurinol[8], all tolerated febuxostat treatment, except 1 patient who developed biopsy-confirmed leukocytoclastic vasculitis.

For those patients with allergy to febuxostat, 2 reports[9,10] have documented successful desensitization to febuxostat in a total of 3 patients. However, the *HLA-B*58:01* status was not reported, and the ethnicity of only 1 patient (Malaysian) was described.

A 30-year-old male of Filipino descent with history of asthma, eczema, and partial thyroidectomy presented with recurrent debilitating attacks of gout. Both his father and brother have gout treated with allopurinol. The patient's written informed consent was obtained to publish the material. Because this is a case study, no ethics board approval was required.

In 2007, he was given allopurinol to treat his gout, which he tolerated well for several years. In 2010, buproprion was added to his drug regimen and within 5 days, he developed fever, rigors, sweats, and facial swelling, culminating in generalized exfoliative dermatitis requiring hospitalization and high-dose steroid treatment. It was decided that his presentation of SJS was caused by the allopurinol through a drug-drug interaction with buproprion, or was induced by buproprion. Because drug challenges for drug-induced SJS are contraindicated, he was advised to avoid both allopurinol and buproprion.

His ongoing acute attacks of gout were not well controlled with indomethacin and prednisone, and given the debilitating severity of his gout, he was given febuxostat. Within 24 h, he developed a raised pruritic erythematous maculopapular rash on his trunk, but no other systemic manifestation, no peripheral eosinophilia, and no evidence of end-organ involvement. The rash improved within 2–3 days after stopping febuxostat.

About 4 years later, he requested a re-challenge to febuxostat because he had ongoing functional disabilities and quality of life impairment secondary to gout. He again developed the same raised pruritic erythematous maculopapular eruption, which improved again after discontinuation of febuxostat.

On presentation in 2018, he still had recurrent incapacitating gout attacks treated only with indomethacin, leaving him bedridden. Given this, desensitization to febuxostat was discussed as a possible consideration. Patch testing with febuxostat 10% in petrolatum was negative in duplicate, but his genotyping was positive for *HLA-B*58:01*. Given his positive *HLA-B*58:01* genotype, ethnicity, history of SJS possibly secondary to allopurinol, and repeated morbilliform skin reactions to febuxostat, he was extensively counseled on the high possibility of life-threatening SCAR, including recurrence of SJS, DRESS syndrome, vesiculobullous reaction, or exfoliative dermatitis, among others. He accepted the risks given the impairment to his quality of life. Informed consent was signed. He underwent a desensitization protocol as outlined in Table 1, which was uneventful. After 7 months of taking a stable maintenance dose of febuxostat 80 mg daily, he had no adverse drug reactions and no further attacks of gout.

Patients with a previous history of SJS with the *HLA-B*58:01* genotype and subsequent allergy to febuxostat may safely undergo desensitization to the latter drug, if necessary, for ongoing management of gout.

Table 1. The febuxostat desensitization protocol.

Day	Concentration, mg/ml	Volume, ml	Amount, mg
1	0.1	0.1	0.01
2	0.1	0.2	0.02
3	0.1	0.4	0.04
4	0.1	0.8	0.08
5	0.1	1.6	0.16
6	0.1	3.0	0.30
7	0.1	6.0	0.60
8	0.1	12.0	1.2
9	0.1	24.0	2.4
10	10	0.5	5.0
11	10	1.0	10.0
12	10	2.0	20.0
13	10	3.0	30.0
14	10	4.0	40.0

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REFERENCES

1. Saito Y, Stamp L, Caudle K, Hershfield M, McDonagh E, Callaghan J, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. Clin Pharmacol Ther 2015;99:36–7.
2. Yu K, Yu C, Fang Y. Diagnostic utility of HLA-B*5801 screening in severe allopurinol hypersensitivity syndrome: an updated systematic review and meta-analysis. Int J Rheum Dis 2017;20:1057-71.
3. Khanna D, Fitzgerald J, Khanna P, Bae S, Singh M, Neogi T, et al; American College of Rheumatology. 2012 American College of

Rheumatology Guidelines for Management of Gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res 2012;64:1431–46.
4. Jutkowitz E, Dubreuil M, Lu N, Kuntz K, Choi H. The cost-effectiveness of HLA-B*5801 screening to guide initial urate-lowering therapy for gout in the United States. Semin Arthritis Rheum 2017;46:594-600.
5. US Food and Drug Administration. Table of pharmacogenomic biomarkers in drug labeling. December 2018. [Internet. Accessed April 15, 2019.] Available from: www.fda.gov/downloads/Drugs/ScienceResearch/UCM578588.pdf
6. Lien YH, Logan JL. Cross-reactions between allopurinol and febuxostat. Am J Med 2017;130:e67-8.
7. Yu K, Lai J, Hsu P, Chen D, Chen C, Lin H. Safety and efficacy of oral febuxostat for treatment of HLA-B*5801-negative gout: a randomized, open-label, multicentre, allopurinol-controlled study. Scand J Rheumatol 2016;45:304-11.
8. Chohan S. Safety and efficacy of febuxostat treatment in subjects with gout and severe allopurinol adverse reactions. J Rheumatol 2011;38:1957-9.
9. Sulaiman N, Othman A, Shahril N, Rashid A, Noh M. Successful febuxostat desensitization in a patient with febuxostat hypersensitivity: a Malaysian experience. SAGE Open Med Case Report 2017;5:1-3 Rep.
10. Di Paolo C, Minetti S, Mineni M, Inverardi S, Rizzini FL, Cinquini M, et al. Desensitization to febuxostat: report of two cases. J Allergy Clin Immunol Pract 2015;3:633-6.

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