Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel

Sima Halevy, MD,[a] Pierre-Dominique Ghislain, MD,[b] Maja Mockenhaupt, MD, PhD,[c] Jean-Paul Fagot, PharmD,[d] Jan Nico Bouwes Bavinck, MD, PhD,[e] Alexis Sidoroff, MD,[f] Luigi Naldi, MD,[g] Ariane Dunant, MS,[b,h] Cecile Viboud, PhD,[d] and Jean-Claude Roujeau, MD,[b] for the EuroSCAR Study Group
Beer-Sheva, Israel; Créteil, Paris, and Villejuif, France; Freiburg, Germany; Leiden, The Netherlands; Innsbruck, Austria; and Bergamo, Italy

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare severe cutaneous adverse reactions.

Objectives: We sought to update knowledge on the causes of SJS or TEN with a focus on the rate of allopurinol-associated cases and to identify risk factors for allopurinol-associated SJS or TEN.

Methods: We conducted a multinational case-control study.

Results: In all, 379 patients with severe cutaneous adverse reactions validated as SJS or TEN and 1505 matched hospitalized control subjects were enrolled. Allopurinol was the drug most frequently associated with SJS or TEN, with 66 exposed patients (17.4%) and 28 exposed control subjects (1.9%) (adjusted odds ratio = 18, 95% confidence interval: 11-32). Allopurinol use was greater than in a previous case-control European study. Daily doses equal to or greater than 200 mg were associated with a higher risk (adjusted odds ratio = 36, 95% confidence interval: 17-76) than lower doses (adjusted odds ratio = 3.0, 95% confidence interval: 1.1-8.4). The risk was restricted to short-term use ($\leq$ 8 weeks). The use of comedications did not increase the risk.

Limitations: Nonsystematic recording of the indications for allopurinol use was a limitation.

Conclusions: Results of this multinational study (EuroSCAR) revealed that allopurinol is the drug most commonly associated with SJS or TEN. The incidence of allopurinol-associated SJS or TEN has increased possibly because of increased use and dosages of this drug. (J Am Acad Dermatol 2008;58:25-32.)

From the Department of Dermatology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva[a]; Reference Center for Toxic and Autoimmune Blistering Diseases, Department of Dermatology, Hôpital Henri Mondor, Créteil, Paris XII University[b]; Dokumentationszentrum schwerer Hautreaktionen (dZh), Department of Dermatology, University Medical Center, Freiburg[c]; Inserm U 444, Faculté de Médecine St Antoine, Paris[d]; Department of Dermatology, Leiden University Medical Center[e]; Department of Dermatology and Venereology, Medical University of Innsbruck[f]; GISED Study Center, Department of Dermatology, Azienda Ospedaliera Ospedali Riuniti di Bergamo[g]; and Biostatistics and Epidemiology Unit, Institut Gustave-Roussy, Villejuif.[h]

Dr Ghislain is currently affiliated with St-Luc University Hospital, UCL, Brussels, Belgium, and Dr Viboud is currently affiliated with Fogarty International Center, National Institutes of Health, Bethesda, Maryland.

Supported by the following institutions/companies (unrestricted grants): ADIR and Cie, Bayer Pharma/AG/Vital, Boehringer Ingelheim, Cassenne, Ciba Geigy/Novartis, Cilag GmbH, Dr Willmar Schwabe, Goedecke Parke Davis, Glaxo Wellcome/Glaxo Smith-Kline, Hoechst AG/Hoechst Marion Roussel/Aventis, Hoffmann-La-Roche, IRIS Servier, Jouveinal Lab, LEO, LILLY, MSD Sharp and Dohme, Pfizer, Rhone Poulenc Rorer, Sanofi Winthrop/Sanofi Synthelabo GmbH, and Schering AG. Funding from pharmaceutical companies in France was managed through contract with Institut National de la Santé et de la Recherche Médicale, French Ministry of Health (PHRC AOM 98027).

Conflicts of interest: None declared.

Previously presented as: Roujeau JC, Ghislain PD, Mockenhaupt M, Bouwes Bavinck JN, Naldi L, Sidoroff A, Halevy S, Paty C. Dose-effect relation in SJS or TEN related to allopurinol. 5th International Congress on Cutaneous Adverse Drug Reactions, Satellite Congress of the 32nd ESDR Annual Meeting, Palexpo Geneva, Switzerland, September 18-19, 2002 [abstract]. J Invest Dermatol 2002;119:725; and Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Schlingmann J, Roujeau JC. Allopurinol is the medication most frequently associated with Stevens-Johnson syndrome or toxic epidermal necrolysis in Europe. International Investigative Dermatology (IID-03), Fontainebleau Hilton, Miami Beach, Florida, April 30-May 4, 2003 [abstract]. J Invest Dermatol 2003;121:72.

Accepted for publication August 9, 2007.

Reprint requests: Sima Halevy, MD, Department of Dermatology, Soroka University Medical Center, Beer-Sheva 84101, Israel. E-mail: halevy@bgu.ac.il.

Published online October 8, 2007.

0190-9622/$34.00

doi:10.1016/j.jaad.2007.08.036

Abbreviations used:

CI:	confidence interval
NSAID:	nonsteroidal anti-inflammatory drug
OR:	odds ratio
SCAR:	severe cutaneous adverse reactions
SJS:	Stevens-Johnson syndrome
TEN:	toxic epidermal necrolysis

Allopurinol, an inhibitor of xanthine oxidase, is an effective uric acid–lowering drug.[1] Most of allopurinol's activity is a result of the metabolite oxypurinol, a noncompetitive inhibitor of xanthine oxidase that prevents oxidation of xanthine to uric acid.[1] Allopurinol has been implicated repeatedly in life-threatening severe adverse drug reactions including hypersensitivity syndrome, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).[2,3]

SJS and TEN are rare, life-threatening, bullous cutaneous diseases generally considered as immune-mediated reactions to drugs. These severe cutaneous adverse reactions (SCAR) are characterized by epidermal necrosis, extensive detachment of the epidermis, erosions of mucous membranes and severe constitutional symptoms. There is evidence that SJS and TEN are a single disease with common causes and mechanisms.[4,5] They differ mainly in the extent of detachment, which is limited in SJS (<10% body surface area), more widespread in TEN (>30%), and in-between in SJS/TEN overlap (10%-30%). Although rare (2 cases/million population/y), SJS and TEN have a significant impact on public health in view of their high mortality (20%-25%) and morbidity.[6]

In a previous case-control study (SCAR study),[7] the risk of SJS or TEN in relation to the use of medications was assessed in 4 European countries from 1989 to 1993. Allopurinol treatment was recorded in 13 of 245 patients with SJS or TEN (5.3%) and in 11 of 1147 control subjects (1%).[7] At that time, allopurinol was used less frequently by patients with SJS or TEN than other high-risk medications such as anti-infectious sulfonamides (especially cotrimoxazole), phenobarbital, oxicam-type nonsteroidal anti-inflammatory drug (NSAID), chlormezanone, and carbamazepine.[7] Based on the study results, regulatory agencies decided on withdrawal of chlormezanone from the market and restricted indications for cotrimoxazole and phenobarbital. Yet, allopurinol is still widely used in spite of its well-known association with SCAR. Furthermore, new indications for the use of allopurinol in cardiovascular diseases have been approved over the course of recent years.[8] Accordingly, the risk of allopurinol-associated SJS or TEN was re-evaluated in a new European case-control study (EuroSCAR) conducted from 1997 to 2001.[9]

METHODS

Design

The EuroSCAR study, a European case-control surveillance of SCAR, was conducted in 6 countries (Austria, France, Germany, Israel, Italy, and the Netherlands) between April 1997 and December 2001. Patients were actively detected in a network of about 1800 hospitals covering about 100 million inhabitants. Included were patients who developed the adverse reaction in the community, outside the hospital, and who were admitted because of symptoms of SCAR. For each case 3 hospital control subjects were matched on age, sex, region, and date of interview. They were selected according to a predefined list of admission diagnoses relating to acute conditions including infections (eg, pneumonia), trauma (eg, fractures), and abdominal emergencies (eg, appendicitis, ruptured ovarian cyst, strangulated hernia) that did not occur as a complication of an underlying chronic disease. We verified that our control group adequately represented the population[10] in terms of prevalence of chronic disease and exposure to medications in common use (eg, benzodiazepines and drugs for diabetes mellitus [data not shown]). After obtaining informed consent from the study participants, trained investigators conducted personal interviews of patients and control subjects (by direct contact) with a structured questionnaire that included clinical data and information on medical history, infection, and drug exposure in the 4 weeks before hospitalization.

The internal review board (Helsinki committee) of each of the participating centers in each country approved the study.

Validation of patients and control subjects

An international expert committee, composed of the 6 national study coordinators (all dermatologists) who were blinded to information on drug exposure and other risk factors validated the patients by reviewing the clinical data, photographs (available for 93% of patients), and results of the pathologic slides (available for 75% of patients). The patients were validated by means of a predefined scoring system, which consisted of clinical and histopathologic parameters (ie, presence of mucous membrane erosions, skin detachment, epidermal sheets, atypical target lesions or spots, a positive Nikolsky's sign, and epidermal necrosis). The expert committee also determined the date of onset of the disease (probable index day) and checked the validity of control