REFERENCES

1 Wada M. [Anti-tuberculosis chemotherapy.] *Kekkaku* 2007; 82: 771–81. (In Japanese)
2 Saito W, Nagayama N, Miyamoto M et al. [Characteristics and treatment outcomes of INH-resistant or RFP-resistant tuberculosis.] *Kekkaku* 2003; 78:611–7. (In Japanese)
3 Chan ED, Laurel V, Strand MJ et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2004; 169:1103–9.
4 Seung KJ, Gelmanova IE, Peremitin GG et al. The effect of initial drug resistance on treatment response and acquired drug resistance during standardized short-course chemotherapy for tuberculosis. *Clin Infect Dis* 2004; 39:1321–8.
5 Anunnatsiri S, Chetchotisakd P, Wanke C. Factors associated with treatment outcomes in pulmonary tuberculosis in northeastern Thailand. *Southeast Asian J Trop Med Public Health* 2005; 36:324–30.
6 Wells CD, Cegielski JP, Nelson LJ et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. *J Infect Dis* 2007; 196(Suppl 1):S86–S107.
7 Cox H, Kebede Y, Allamuratova S et al. Tuberculosis recurrence and mortality after successful treatment: impact of drug resistance. *PLoS Med* 2006; 3:e384.

Allopurinol and the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis

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

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SUMMARY

The EuroSCAR study, a European case-control surveillance of severe cutaneous adverse reactions (SCAR), was conducted in six countries (Austria, France, Germany, Israel, Italy and the Netherlands) between April 1997 and December 2001. Patients were actively detected in a network of about 1,800 hospitals covering about 100 million inhabitants. Included were patients who developed an adverse reaction in the community, outside the hospital, and who were admitted because of symptoms of SCAR. For each case, three hospital control subjects were matched on age, sex, region and date of interview. An international expert committee, composed of the six 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 (i.e. the 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 subjects, based on the admission diagnosis and the date of onset of their acute condition. Odds ratio (OR) and 95% confidence interval (CI) were estimated by standard methods (SAS, Version 9.1, SAS Institute Inc, Cary, NC, and StatXact-5, Cytel Software Corporation, Cambridge, Mass.). The duration of drug exposure was classified as either ≤8 weeks or >8 weeks before the index day.

Of 513 potential patients with Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) who were interviewed, 379 'community-acquired' patients were analysed (SJS 134; SJS/TEN overlap 136; TEN 109). A total of 1,763 control subjects were interviewed, of whom 1,505 were enrolled in the study. Allopurinol was the high-risk drug most frequently associated with SJS or TEN, with 66 exposed patients (17.4%) and 28 exposed control subjects (1.9%) (adjusted OR=18, 95% CI: 11–32). Other drugs implicated, in decreasing order, were carbamazepine (8.2%), cotrimoxazole (6.3%), nevirapine (5.5%), phenobarbitol (5.3%), phenytoin (5%), and lamotrigine (3.7%).

The doses of allopurinol were higher in patients with SJS or TEN (median 300 mg/d, mean 258 ± 66 mg/d) compared with control subjects (median 150 mg/d,

mean 189 ± 95 mg/d; p=0.001). The difference persisted when calculated per kilogramme of body weight. A daily dose of 200 mg or more of allopurinol was associated with an increased risk for SJS or TEN (adjusted OR=36, 17–76) compared with lower daily doses (3.0, 1.1–8.4). There was no association between the severity of illness, as manifested by the maximal erythema, the maximal detachment of the epidermis or death, and the daily dose of allopurinol. The risk for SJS or TEN was restricted to recent users (≤8-week interval between initiation of treatment and onset of reaction). For short-term use of allopurinol the unadjusted OR was 261 (36–∞), but there was no significant risk for long-term use (>8 weeks) (adjusted OR 0.9, 0.3–2.4).

The majority of the 56 patients recently exposed to allopurinol (33 of 56 or 59%) were female. The patients were significantly older than those with SJS or TEN not exposed to allopurinol (64 ± 16 and 44 ± 25, respectively, p <0.0001). There was no significant difference between patients and control subjects in the total number of concomitant medications (mean 6.9 and 6.6, respectively; median 7.0 and 5.5, respectively). Comorbidity rates with renal dysfunction, any infection, malignancy, collagen vascular disease, diabetes mellitus or atopic dermatitis did not differ significantly between patients and control subjects.

OPINION

Stevens-Johnson syndrome and TEN are rare, life-threatening, bullous mucocutaneous diseases, generally considered to be immune-mediated reactions to drugs. They are characterised by epidermal necrosis, extensive detachment of the epidermis, erosions of mucous membranes and severe constitutional symptoms. Stevens-Johnson syndrome and TEN are probably a spectrum of the same disease. They are classified mainly in the extent of involvement, which is limited in SJS (<10% body surface area), more widespread in TEN (>30%) and in-between in SJS/TEN overlap (10–30%). Despite being rare (about two cases per million population a year), SJS and TEN have a significant impact on public health in view of their high mortality (20–25%) and morbidity.

Data from the EuroSCAR study suggest that allopurinol, recorded in 17.4% of 379 patients and 1.9% of 1,505 control subjects (adjusted OR=18, 95% CI: 11–32), is the most common drug associated with SJS or TEN in Europe and Israel.

It is interesting to note similar findings in Malaysia, Singapore and Taiwan. A study by Yap et al. in Malaysia found that 20.8% of 24 cases of both SJS and TEN were due to allopurinol.[1] In Singapore, from 2003 to 2007, allopurinol was the most common cause of both SJS and TEN, being the implicated drug in 13 of 85 cases (15.3%).[2] A similar case-control study conducted in a hospital in Taiwan also showed allopurinol exposure in 17% of 35 patients with SJS and TEN and 2% of control subjects. All these data suggest that allopurinol plays a major role in the induction of SJS and TEN in the Asian population. In Han Chinese and Japanese patients as well, the HLA-B5801 allele was strongly associated with severe cutaneous adverse reactions caused by allopurinol.[3,4]

The EuroSCAR study also found that a daily dose of 200 mg or more of allopurinol was associated with an increased risk for SJS or TEN compared with lower daily doses. The risk for SJS or TEN was restricted to recent users (≤8 weeks). Most of allopurinol's activity is the result of the metabolite oxypurinol, which is a noncompetitive inhibitor of xanthine oxidase that prevents the oxidation of xanthine to uric acid. Although comorbidity rates with renal impairment did not differ significantly between the patients and the control subjects, dosing should also be based on the renal function as oxypurinol excretion is dependent on the renal function.

It is prudent to note that in a large proportion of the cases of allopurinol hypersensitivity the indications for initiating allopurinol were frequently unclear. More often than not, the drug is prescribed for asymptomatic hyperuricaemia. Published literature showed that as many as 86% of the cases were due to inappropriate allopurinol prescription.[5] Such inappropriate prescription leads to unnecessary mortality and morbidity from SJS and TEN. In view of the severe adverse reactions experienced with allopurinol, rational prescribing and dosing would help to reduce such life-threatening drug reactions.

REFERENCES

1 Yap FBB, Wahiduzzaman M, Pubalan M. A 4-year retrospective study of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Malays J Dermatol* 2008; 21:35–9.

2 Lee HY, Pang SM, Thamotharampillai T. Allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Am Acad Dermatol* 2008; 59:352–3.

3 Hung SI, Chung WH, Liou LB et al. HLA-B5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* 2005; 102:4134–9.

4 Kaniwa N, Saito Y, Aihara M. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics* 2008; 9:1617–22.

5 Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. *Arthritis Rheum* 1986; 29:82–7.