Editorial

HLA-B*58:01 is not the only risk factor associated with allopurinol-induced severe cutaneous adverse drug reactions

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Allopurinol is the main cause of severe and life-threatening non-immediate cutaneous adverse drug reactions (CADR) worldwide (1-4). There is therefore an urgent need to know the main risk factors in order to establish preventive measures and reduce the number of severe cases. They are associated with a significant burden for the health system in which concerns direct costs of treatment of the reaction itself (intensive care or burn units for toxic epidermal necrolysis (TEN) or liver transplantation in severe cases of DRESS/DIHS (drug reaction with eosinophilia and systemic symptoms or drug-induced hypersensitivity syndrome) and indirect costs related to fatalities and permanent sequelae (autoimmune diseases following DRESS or ocular and genital sequelae from TEN) (5,6).

Allopurinol has been particularly associated with maculopapular exanthema (MPE), DRESS and the exanthematic necrolysis type of drug eruptions [Stevens-Johnson syndrome (SJS)/TEN] (4) and less frequently with fixed drug eruption (FDE) or acute generalized exanthematous pustulosis (AGEP). These are all delayed-type hypersensitivity reactions with T cells specifically recognizing allopurinol or its metabolite, oxypurinol. The main drug-specific effector T cells may belong to different subphenotypes (CD4+, CD8+, Th1, Th2, Th17), which produce their own cytokines and effector molecules in different amounts, therefore justifying the wide diversity of clinical and histologic patterns of CADR (6).

CD8+ T cells rich in granulysin which is a potent cytotoxic mediator involved in SJS/TEN (7) and DRESS (8), recognize the drugs or their metabolites in a HLA-I restricted manner. They recognize the HLA modification that occurs either by direct drug combination with the HLA-I antigen-binding site and/or with the endogenous peptides that usually fit in its groove (9,10). Therefore, for some drugs and some CADR, specific HLA molecules confer a high risk for severe drug eruptions. HLA-B*57:01 is strongly associated with abacavir hypersensitivity syndrome world-wide and after pre-testing recommendation this adverse reaction is almost completely abolished (11). HLA-B*15:02 is associated with carbamazepine-induced SJS/TEN only in Han Chinese and since the recommendation to test for HLA before initiating therapy in Taiwan there was a dramatic reduction in these reactions, although with an increase for SJS/TEN from other anticonvulsants with no recommendation for HLA-pretesting (12,13).

HLA-B*58:01 has also been strongly associated with the risk of allopurinol-induced severe cutaneous adverse reactions (SCAR), but it is not so straightforward how allopurinol or oxypurinol bind to the HLA molecule and how it will sensitize and stimulate T cells, compared to the very detailed knowledge of the binding of carbamazepine and abacavir to the respective HLA molecules (9,13,14). Contrary to carbamazepine whose association to HLA-B*15:02 is limited to SJS/TEN, in allopurinol the risk is extensive both to SJS/TEN and DRESS (2) and possibly also for the less severe MPE (15,16). Similarly to carbamazepine, where HLA-B*15:02 confers risk for Han Chinese and not for Europeans or Japanese, for whom HLA-A*31:01 is the major association) (17,18), there is a

strong ethnic influence on the relation between allopurinol-induced SCAR and HLA-B*58:01.

Actually, HLA-B*58:01 has been associated with allopurinol induced SJS/TEN and DRESS since the studies by Chan and Tan in southern Chinese in 1989 (19) with a strong association further supported by Hung *et al.* in 2005 in Han Chinese in Taiwan (20) and later in Han Chinese from China, Thailand, Hong Kong, Korea and those living in Australia (3), with an associated risk between 34.00 and 696.0 (16). This association is less strong in Japan where only 36–40% of allopurinol induced SCAR patients are HLA-B*58:01 positive, or in European Caucasian patients where only 55–64% of patients with SJS/TEN or DRESS carry this allele (2,3,21). Although the frequency of HLA-B*58:01 in different populations varies significantly (up to 20% in Taiwan and less than 2% in Europeans) (2,21) which a consequent influence on the frequency of severe SCAR in the different populations, racial/ethnicity also seems to have some influence on the capacity to develop this reaction. Actually the percent of HLA-B*58:01 negative individuals with allopurinol-induced CADR is higher in European Caucasians and Japanese, suggesting other possible risk factors. HLA-B*58:01 positive individuals tolerating allopurinol are also more common in Europeans than in Han Chinese, reinforcing a much stronger association between HLA-B*58:01 and allopurinol in Asian populations (22). In the *Annals of Rheumatic Diseases*, in a large study performed in the USA, Keller *et al.* also showed a strong influence of racial/ethnicity in allopurinol-induced severe CADR (23). They showed that apart from Asians, Black Americans as well as Native Hawaiian/Pacific Islander also have a higher risk for allopurinol-induced SCARs compared to white and Hispanic Americans. Although they did not evaluate HLA-B*58:01 in patients with allopurinol-induced SACR, the frequency of this SCAR is in agreement with the high prevalence of this HLA haplotype in the US blacks (2.6–6.4%), African population (7–10%) and US Pacific Islanders (5.8%) compared to the white Americans (<1% to 1.9%). Interestingly these same groups who have increased risk for developing SCAR also showed increased mortality from this reaction (23), suggesting that the association with HLA-B*58:01 is associated both with an increased risk and severity of the disease.

Apart from HLA-B*58:01 other factors may influence the risk of developing a SCAR from allopurinol. Asymptomatic hyperuricemia and concomitant use of diuretics, reported in many studies (2), were not confirmed by Keller *et al.* An initial dose of allopurinol >100 mg/day or a concomitant kidney disease associated with a reduced clearing of allopurinol and its metabolite oxypurinol, were confirmed as additional risk factors (5,23,24). This may also be the explanation for an increased risk in a higher age (>60 years) with an expected reduced renal clearing of allopurinol/oxypurinol (23). Additionally, both age, chronic kidney disease and high initial dose of allopurinol were associated with increased mortality from allopurinol-induced-SCAR (23). In a recent study, Chung *et al.* found that a higher initial or maintenance allopurinol doses were not so important in the initiation of the SCAR, but they were mostly related with a worse prognosis. Actually higher and sustained plasma levels of oxypurinol after allopurinol withdrawal were associated with higher granulysin levels and worse prognosis in both DRESS and SJS/TEN (25). This is also in agreement with *in vitro* studies showing that a high dose of allopurinol/oxypurinol or prolonged stimulation may also be necessary for the sensitization/activation of the specific T cells clones with preferential TCR (24).

Moreover, Keller *et al.* found that the female sex was independently associated both with a higher frequency of allopurinol-induced SCAR and a higher mortality, particularly if females were older and belonging to high risk ethnical groups. Gonçalo *et al.* also found more SCAR from allopurinol in females and, particularly in DRESS, the association with HLA-B*58:01 was stronger than in males (81% in females *vs.* 38% in males) (2), which may be in agreement with an increased risk for females also in Caucasians. Apart from other few studies, female sex is not usually reported as a high-risk group but it is an interesting observation as allopurinol is used mostly in males who most frequently suffer from hyperuricemia and gout.

In conclusion, all studies are in agreement with the strong association with allopurinol-induced SCAR and HLA-B*58:01 that is much more significant in patients with an Asian (non-Japanese) or African descent who, moreover, seem to have a worse prognosis. Actually, in our previous study and from our experience with in-patients we seldom experience fatalities from allopurinol-induced DRESS, which may be associated with our almost exclusive Caucasian population and low prevalence of HLA-B*58:01. How ethnicity can influence frequency and prognosis of these SCAR, beyond HLA-B*58:01, is not yet completely understood.

Therefore, as allopurinol is not usually a medication to be used in urgent situations, as is the case of some anticonvulsants, and there are alternative drugs that can be

used with lower risk in these populations, HLA-B*58:01 testing before initiating allopurinol should be done at least in high risk ethnic groups, as already recommended in previous studies (3,5,16,19). Moreover it has been shown to be cost-effective (5). With this study we should probably reinforce this recommendation for older populations, particularly females. If HLA testing cannot be done, at least a recommendation should reinforce the need to use of lower initial doses of allopurinol, have a good evaluation of kidney function and, especially if it is a case of asymptomatic hyperuricemia, think twice before initiating allopurinol.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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