Reviewer's report

Title: Association of HLA-B*5801 Allele and Allopurinol-Induced Stevens Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis

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Reviewer: Maja Mockenhaupt

Reviewer's report:

With the manuscript entitled “Association of HLA-B*5801 Allele and Allopurinol-Induced Stevens Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis” the authors reviewed several earlier studies performed in this field. My questions and comments to the manuscript are the following:

Background:

1. When reporting the incidence of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), the authors refer to one retrospective study performed two decades ago in Singapore and a review paper not focusing on the calculation of incidence. However, there have been reports on prospective registries leading to reliable incidence rates for SJS and TEN such as Rzany et al, J Clin Epidemiol, 1996 and Mockenhaupt, Norgauer, ACI, 2002. The latter publication also provides demographic data including mortality.

2. When speaking about medications with a risk to induce SJS/TEN, the authors refer to Halevy et al 2008. However, this paper mainly reports on allopurinol which is actually the only uric acid lowering agent with a risk for SJS/TEN, but not on other medication. The reference for the multinational case-control-study the authors are mentioning is missing: Mockenhaupt et al, J Invest Dermatol, 2008.

Methods:

1. The criteria for case classification are based on a consensus definition published by an international group of dermatologists in 1993. Actually, the authors refer to this publication, but they do not provide all authors. Roujeau was one of the co-authors of this publication, but nevertheless the criteria should not be referred to as “Roujeau’s criteria”, but as the consensus definition. In reference 11, Roujeau only summarizes the information of the earlier original publication of Bastuji-Garin et al.

Results:

1. The authors are speaking about “Japan Severe Adverse Reaction (JSAR) research group. If I understood the Japanese colleagues correctly in their presentation at international meetings, they call their group “JSCAR”.
2. I find it difficult to consider a meta-analysis of four studies a scientific breakthrough. In contrast, I am afraid that rather clear findings of these four studies are somewhat diluted by the results of the meta-analysis.

Discussion:

1. The first sentence of the discussion should simply be deleted.

2. The authors report about “several strengths” of their study, but what about the pitfalls?

3. Is it really helpful to combine results of a 100% allele frequency of HLA-B*5801 and allopurinol-induced SJS/TEN in Han-Chinese and 55% of allele frequency in Europeans?

4. On page 15 of their manuscript the authors suggest different hypotheses related to the pathomechanism of SJS/TEN. However, it has to be clearly stated that this is hypothetic and not proven.

5. The authors suggest that genotype testing of the HLA-B allele may be beneficial for patients before receiving the drug. This had already been known for Han-Chinese populations before receiving allopurinol (or carbamazepine) but I doubt the benefit for patients of European decent due to low allele frequency and only 55% HLA-B*5801 expression in allopurinol-induced cases of SJS/TEN.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests