Subject: BMJ - Decision on Manuscript ID BMJ.2015.025516.R1

Body: 28-Jul-2015

Dear Dr. Shen:

Manuscript ID BMJ.2015.025516.R1 entitled "HLA-B*58:01 genotyping to prevent allopurinol-induced severe cutaneous adverse reactions: national prospective study" which you submitted to BMJ,

Thank you for sending us this paper and giving us the chance to consider your work, which we enjoyed reading.

Decision: We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to revise it according to the statistician and the reviewers comments: we are provisionally offering acceptance but will make the final decision when we see the revised version.

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Yours sincerely

Dr Tiago Villanueva
Assistant Editor
tvillanueva@bmj.com,

Reviewer: 1

Recommendation:

Comments:
The authors have responded to the suggestions that I made in previous report appropriately.

I will point out three things to quickly improve statistical presentation:

1) include in 95% CI for the prevalence of adverse reactions in the abstract as well as the text
2) add 95% CIs to the rates in Table 3 for the historical data
3) present the P-values in Table 1 to 2 decimal places.

Additional Questions:
Please enter your name: Jon Deeks

Job Title: PRofessor of Biostatistics

Institution: University of Birmingham

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
Comment on author's responses to the points raised 5 July 2015

I am restricting my note to the responses made to my own earlier specific comments

1. The distinction between DRESS, SJS, and TEN

This point has been adequately addresses

2. Justification for the use of 2001-2004 data instead of more recent data

The authors suggest that this decision was based on their concern that more recent data could be biased. Since their prior publication, some clinicians had started HLA-B*58:01 testing prior to prescribing allopurinol. I would have thought that at least a sensitivity testing using more recent data would have been informative.

3. The possibility that a two-month long follow-up is too short given other reports of a longer time lag between exposure and adverse reaction.

The authors use internal validation to counter external reports of longer lag times. 'Typical latency' for rare events is not a robust estimate of the range. However, their follow-up data suggest that the 2 month period is probably acceptable. So this point has been addressed satisfactorily.

4. Cost-effectiveness analysis (CEA)

Deferring the CEA is I think the right decision

5. Data used in the pharmacoeconomic analysis

Point addressed satisfactorily

6. Generalisation of their inferences to other populations

I agree that the authors' inferences may be applicable to other populations. 'May be' however does not mean 'are'. The available evidence for other populations is rather sparse, particularly for subjects of European descent. Although I am aware that there are guidelines that state 'HLA-B*58:01 screening may be beneficial in a subset of high-risk patients (e.g. chronic renal failure', as far as I can ascertain the evidence-base for this is very weak. There are two distinct suppositions to this: (i) that hypersensitivity to allopurinol is more common in chronic renal failure patients and (ii) HLA-B*58:01 co-segregate with chronic renal failure. The literature cited in support of the guideline recommendation is a study that provides no strong support for either (i) or (ii). My view is still that the authors should be more cautions about claims of generalisability beyond Han Chinsese and possibly Thai and Koreans. However, extension to other populations such as the Japanese or Europeans is not justifiable on the available data.

My concern is that if HLA-B*58:01 becomes perceived as necessary prior to prescribing allopurinol in populations for whom there is little supporting data, many to whom such testing is not available would be deterred from prescribing, possibly the best drug in its therapeutic class. As the authors themselves suggests endorsement of the BMJ could lead to uncritical use and unjustifiable promotion of the approach. Editing by the BMJ may help overcome this concern.

In conclusion:

I would be happy for the paper to be published in the BMJ but to me point 6 is not sufficiently well addressed as the text stands.

Additional Questions:
Please enter your name: Alain Li-Wan-Po

Job Title: Director

Institution: Centre For Evidence-Based Practive Ltd

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 3

Recommendation:

Comments:
The authors have responded adequately to the comments raised by the Editors and Reviewers, and I agree with removing the cost-effectiveness data from this manuscript.

The only remaining comment I have is regarding the Conclusion statement in the abstract as it is currently not very clear (and is an important component of the manuscript). I suggest revision for clarity.

An example to consider:'Prospective screening of the HLA-B*58:01 allele coupled with an alternative medication for carriers significantly decreased the incidence of allopurinol-induced SCARs.'

Additional Questions:
Please enter your name: Stuart A. Scott, PhD

Job Title: Assistant Professor

Institution: Icahn School of Medicine at Mount Sinai

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Date Sent: 28-Jul-2015