Subject: BMJ - Decision on Manuscript ID BMJ.2015.025516

Body: 25-May-2015

Dear Dr. Shen

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

Thank you for sending us this paper, which we were pleased to have the chance to consider and enjoyed reading. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it. This is because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript committee meeting, so that we will be in a better position to understand your study and to decide whether The BMJ is the right journal for it.

Many thanks again. We look forward to seeing your revised article within a month and, we hope, to reaching a decision.

** THE REPORT FROM THE MANUSCRIPT COMMITTEE MEETING, REVIEWERS' REPORTS, AND THE BMJ'S GENERAL REQUIREMENTS FOR RESEARCH PAPERS ARE AVAILABLE AT THE END OF THIS LETTER.**

First, however, please read these four important points about sending your revised paper back to us:

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Yours sincerely

Dr Tiago Villanueva
Assistant Editor
tvillanueva@bmj.com

As well as submitting your revised manuscript, we also require a copy of the manuscript with changes highlighted. Please upload this as a supplemental file with file designation 'Revised Manuscript Marked copy'.

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INFORMATION ON REVISING THE CONTENT AND FORMAT OF YOUR ARTICLE

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript. Members of the Committee were:

Elizabeth Loder (chair), Jon Deeks (statistician), Rebecca Burch, Wim Weber, Jose Merino, Rubin Minhas, Kristina Fister, Tiago Villanueva

Decision: request revisions

Detailed comments from the meeting:
First and foremost, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

Our statistician made the following comments:
The authors report an historically controlled study looking at the incidence rate of allopurinol-induced severe cutaneous adverse reactions in a cohort of patients who are stratified for drug choice by HLA-B*58:01 genotyping. They show convincingly that avoiding use of allopurinol in people who tested positive for the HLA-B*58:01 allele. I have some comments on the presentation and statistical analysis.

1) The authors only followed participants for two months. Could they please provide stronger evidence and data supporting that adverse events are likely to occur within 2 months? (the current phrase is that "in general SCARs onset occurs within 2 months" which is not particularly convincing that all cases would have been detected). It would seem a weakness of the study not to have followed-up individuals for a longer time period, particularly seeing that the control group data are based on 3-monthly prescriptions.

2) The power calculation is written as if the comparison is being made between a known fixed value of 0.3% and a hypothesised value of 0.03% to be estimated within the sample. Given that the comparison is known and estimated with high precision this seems reasonable. However, the computed sample size does not agree with this (my sample size calculator using a normal approximation suggests that the stated sample size of 2169 would have 85.8% power (not the 99% stated). Could the authors fully justify and explain their calculation.

3) The statistical method the authors state has been used is a Fisher's Exact test. This is a two group test and requires data from both the screening cohort and the comparison group. It is not clear what data has been used for the comparison group in the analysis presented in the paper. However, in line with point 2) the comparison between the observed result in the collected cohort and the historical figure of 0.3% might be better based on a one sample Binomial test (to work out the probability that the see whether the observed incidence rate differs from the fixed value of 0.3%). My estimate of the associated P-value from this test is 0.0003 – thus similar to that reported by the authors.

4) It is important that the authors report the 95% confidence interval for the observed event rate in the cohort – (0% to 0.13%) as this gives an upper limit on the observed event rate.

- The statistical methods here are not quite right – both for the power calculation and the comparison, but it makes no difference to the conclusions which would have been drawn. This is a "one sample" study which compares the observed rate to a fixed known value (0.3%), and an appropriate "one sample" sample size calculation should have been done (they have overestimated power in their calculation) and comparison of the observed to a fixed value using a binomial test (which gives nearly the same P-value).
- The economic analysis does not provide enough detail to be helpful.

- One editor wondered about the large number or authors and whether they all met authorship criteria.

He also wondered whether results applied to people who are not of Han Chinese descent. Non-Han people were excluded from the study. Does this limit the generalizability of the findings? In the US, most physicians will identify patients of Chinese descent but he doesn't think they would differentiate the different ethnicities. Would a physician starting allopurinol ask for this information? Is genomic screening before prescribing allopurinol the standard of care? From the paper, he did not get the sense that it is, even in Taiwan. As such, he felt that doing a RCT is not necessarily unethical and would be better than using historical control data. He felt the economic data should be removed. Finally, he wondered whether the paper is useful, as the association between the presence of HLA-B*58:01 and skin reactions is well known. He felt that without a suitable control group, we cannot draw firm inferences about the clinical impact of screening.

- Another editor felt that the study was useful and that this was an interesting clinical development. However, he felt that the study is nethodologically not strong but still convincing.

- Another editor was supportive and felt that most of the concerns raised in the reviews seem addressable. He added that the time period for selecting the historical controls seemed odd and felt that it should be more recent. Moreover, he considered that the limitations should mention the 2 month follow-up and that a sensitvity analysis could be done to assess the consequences of a longer period of presentation of SCAR's.
He added that the health economic analysis is rather summary and should be removed, unless it is properly done. It would be a stand-alone paper in its own right. The findings of an economic review would support whether this should be routine practice, so the authors should not claim this should be routine practice.

- Finally, another editor did not have a strong feeling about this paper. Nevertheless, she acknowledged that the other papers in this area were well cited, which was one point in favour. She considered that this is a question about standard of care. She felt that the question is not whether it's ethical to give allopurinol to someone who has tested positive for the HLA subtype of concern. The question is whether it's ethical to give it to somebody who hasn't been tested if testing is available.

IMPORTANT
When you revise and return your manuscript, please take note of all the following points about revising your article. Even if an item, such as a competing interests statement, was present and correct in the original draft of your paper, please check that it has not slipped out during revision.

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d. Please include these items in the revised manuscript to comply with BMJ style:

Title: this should include the study design eg "systematic review and meta-analysis"

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structured abstract including key summary statistics, as explained below (also see
http://resources.bmj.com/bmj/authors/types-of-article/research)
for every clinical trial - and for any other registered study - the study registration number and name of register – in the last line of the structured abstract.

Introduction
this should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now

Methods:
for an intervention study the manuscript should include enough information about the intervention(s) and comparator(s) (even if this was usual care) for reviewers and readers to understand fully what happened in the study. To enable readers to replicate your work or implement the interventions in their own practice please also provide (uploaded as one or more supplemental files, including video and audio files where appropriate) any relevant detailed descriptions and materials. Alternatively, please provide in the manuscript urls to openly accessible websites where these materials can be found
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please report statistical aspects of the study in line with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines http://www.equator-network.org/reporting-guidelines/sampl/

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For a clinical trial:
• Absolute event rates among experimental and control groups
• RRR (relative risk reduction)
• NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000)

For a cohort study:
• Absolute event rates over time (eg 10 years) among exposed and non-exposed groups
• RRR (relative risk reduction)

For a case control study:
• OR (odds ratio) for strength of association between exposure and outcome

For a study of a diagnostic test:
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• PPV and NPV (positive and negative predictive values)
one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used
for articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system
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please write the discussion section of your paper in a structured way, to minimise the risk of careful explanation giving way to polemic.Please follow this structure:
statement of principal findings of the study
strengths and weaknesses of the study
strengths and weaknesses in relation to other studies, discussing important differences in results and what your study adds. Whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses (eg Cochrane reviews)
meaning of the study: possible explanations and implications for clinicians and policymakers and other researchers; how your study could promote better decisions
unanswered questions and future research

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What this paper adds/what is already known box (as described at http://resources.bmj.com/bmj/authors/types-of-article/research)

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for studies that are relevant to patients we expect authors to report in their articles the extent of their study's patient-centredness, as highlighted by these questions:
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was the development and/or selection of outcome measures informed by patients' priorities and experiences? Please give details (Methods section)
were patients/service users/carers/lay people involved in developing plans for participant recruitment and study conduct? If so, please specify how (Methods section)
have you planned to disseminate the results of the study to participants? If so how will this be done? (Describe in brief footnote)
are patients thanked in the contributorship statement or acknowledgements?
for articles reporting randomised controlled trials: did you assess the burden of the intervention on patients' quality of life and health? If so, what evaluation method did you use, and what did you find? (Methods and Results sections)

REFEREES COMMENTS

Reviewer: 1

Recommendation:

Comments:
What the authors did

It is now well-established that there is a strong association between the variant allele HLA-B*58:01 and allopurinol-induced severe cutaneous reactions (SCR defined as Drug reaction with eosinophilia and systemic symptoms (DRESSS), Stevens-Johnson syndrome, or toxic epidermal necrolysis). HLA-B*58:01 is found at higher frequencies in Asian populations, notably the Han Chinese population studied by the authors, than in other ethnic groups.

Given that the SCR are potentially lethal, the authors set out to determine whether pre-prescription genetic testing for this variant would be useful for informing the prescribing of allopurinol for patients with hyperuricemia. To this end they undertook a prospective study of HLA-B*58:01 genotyping of a population of allopurinol-naïve subjects requiring uric-acid lowering therapy.

Based on the results they subdivided the patients into two HLA-B*58:01 groups: (i) negative and (ii) positive patients. The first group received allopurinol and the second group, an alternative treatment or their pre-study medication.

All subjects were interviewed by telephone during the 2-month period following initial screening (for HLA-B*58:01–negative subjects) or after the second clinic visit (for HLA-B*58:01–positive subjects) to monitor for symptoms of adverse drug reactions, including SCAR. For comparison they used the incidence rate of SCR (0.30%) based on 2001-2004 data held in the Taiwan National Health Insurance Research Database (NHIRD).

What they found

Of 2910 patients genotyped 571 (19.6%) were HLA-B*58:01-positive. Of the 2173 HLA-B*58:01-negative subjects successfully followed-up, none developed SCAR.

From the results the authors estimated that they would have prevented 7 cases of SCR by not prescribing allopurinol for the HLA-B*58:01–positive patients. They then went on to do a 'cost-effectiveness' analysis using febuxostat as alternative drug and estimated that genotyping is cost-saving to the tune of some $12 million.

What they inferred

The authors concluded that pre-prescription genotyping would be cost-saving and reduce the incidence of SCR to allopurinol.

Referee's assessment

This is a generally well-written report of an interesting prospective study

Points to consider

(i) In the definition of SCR, DRESS was a qualifying presentation. How likely is it that some of the patients with systemic adverse reactions while on allopurinol, reported in Table 2, might in fact have had DRESS? The authors ought to describe what quality control procedures they had in place to make sure that no case is misclassified and not reported? For Stevens-Johnson syndrome, or toxic epidermal necrolysis this is more unlikely given the severity of the phenotype.
(ii) For estimating the number of cases of SCR avoided the authors used rather old 2001-2004 data. Why were more recent data not used to ensure that any misclassification biases are minimised or at least consistent for both their active cohort and the historical cohorts?
(iii) In their database data-trawl, they identified patients who had been on at least 3 months of allopurinol. Yet their follow-up is only of 2-month duration in their prospective study. Given that the time lag between exposure and SCR is rather ill-defined and may be as long as more than 12 weeks (Ramasamy et al. 2013) how confident are they that their allopurinol-treated cohort may not yet develop SCR?
(iv) In their 'cost-effectiveness' study the authors assume equi-effectiveness (beneficial and adverse effects). Comparative data suggests that febuxostat may well have more adverse cardiovascular and hepatic effects profiles (see product label) although the available data are rather sparse. How should trade-offs be made between these adverse effects with febuxostat and potential SCAR with allopurinol? Given this uncertainty, the authors should be more reserved in their claims.
(v) By their own estimates the positive predictive value is only 2%. Given this, the point raised under (iv) is particularly important.
(vi) The authors make inadequately unsupported generalisations about potential use in other populations for which only very limited data are available. I think that they should refrain from this particularly given the lower and/or ill-defined prevalence of the influential allele in those populations.

Overall recommendation

While the study is interesting and worthy of publication the authors should consider the potential problems indicated above more formally in their analysis and discussions than they have done.

Professor Alain Li-Wan-Po
Director
Centre for Evidence-Based Pharmacotherapy
Nottingham NG9 3FD

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

Job Title: Director

Institution: Centre for Evidence-Based Pharmacotherapy

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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Reviewer: 2

Recommendation:

Comments:
The article by Shen and colleagues is an extension of their previous pharmacogenetic discovery and implementation studies, now reporting on their multi-institutional prospective cohort that tested the utility of HLA-B*5801 genotyping to avoid allopurinol-induced SCARs in Taiwan. Out of 2926 enrolled subjects treated with allopurinol, ~20% were HLA-5801 carriers and were counselled to take alternate medication. Clinical follow-up determined that no cases of SCARs occurred in their cohort in either the positive or negative subjects. Based on the historical incidence of allopurinol-induced SCARs in Taiwan, a statistically significant difference in SCARs incidence was detected, indicating that prospective HLA genotyping may have clinical utility and be cost-effective. The manuscript is clearly presented and the study is of very high importance for the pharmacogenetics and personalized medicine fields.

Some comments to consider for possible revision:

Major comments:
1. The entire basis of the conclusion is based on the comparison to the historical incidence of allopurinol-induced SCARs. The authors use data from 2001-2004; however, there is no clear rationale why this time period was selected. A wider selection of time periods, or at least some more recent data are needed to strengthen their findings.
2. The authors include p=0.0026 in the abstract and throughout the manuscript as the primary p value; however, it is not one of the p-values in Table 3 and does not seem to be an average value from their time period. This requires clarification.
3. The estimated incidence of allopurinol-induced SCARs was calculated by SCARs cases divided by annual number of new allopurinol users. The SCARs number was based on ICD-9 code; were any of these cases validated or confirmed manually (or otherwise) to be true allopurinol-induced SCARs and not another drug induced SCARs? Any confirmation data is needed to support these numbers, or if they are not necessary, an explanation as to why not is warranted.
4. The most common medication taken for the positive subjects was benzbromarone. Can the authors include more discussion about the efficacy of this alternative and why these results do not suggest just using this alternative for all gout patients instead of genotype-directed selection? Is this driven by cost differences or efficacy or both?

Minor comments:
1. Citing and commenting on the CPIC guideline for HLA-B/allopurinol in the Introduction is suggested (PMID: 23232549).
2. Introduction, page 7, line 32-35: could be refined to remove the term 'is rather lethal'.
3. Results, page 14, lines 38-39: suggest using 'counseled' instead of 'given advice'.
4. Discussion, page 18, first sentence: suggest rewording, 'prior to' instead of 'before', 'subsequently' instead of 'then', and 'would likely' instead of 'could'.
5. Discussion, second paragraph: suggest 'Our results support HLA...' instead of 'Our results suggest the merit of HLA...'.
6. Discussion, page 20, line 51: suggest removing the word 'culprit'.
7. Discussion, Strengths and Limitations of Study section: appears to be written by a different person. Acronyms are incorrectly re-defined, SCARs is written out incorrectly, etc. Suggest revising this section for consistency.
8. Table 1: Can p-values be included between positive and negative cases for the clinical characteristics?

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

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 3

Recommendation:

Comments:
The manuscript by Ko et al explores the impact of a screening program for HLA-B*58:01 for reducing allopurinol induced severe cutaneous adverse reactions in Taiwan. The manuscript is well written and reports results that are concordant with what could be predicted on the basis of prior studies. With the screening approach no cases of SCARs were identified for 2916 subjects participating in the study. On the basis of a historical control group it was anticipated that there would be 6-7 SCARs.
The result are as anticipated based on prior studied (i.e. (1) individuals carrying a HLA-B*58:01 allele and not using allopurinol will not have SCARs; (2) individual without a HLA-B*58:01 started on allopurinol will not have SCARs [or the risk is very low]). Nonetheless, the study is useful in prospectively confirming the results of prior studies and in demonstrating that a screening approach is feasible to undertake in clinical practice.

The statistical analyses undertaken were relatively simple and appear to be appropriate.

One aspect that is worth clarifying is the approaches used to identify individuals with SCARs. In the historical control group this undertaken on the basis of ICD codes recorded in a national health insurance database, whereas in the prospective cohort it was determined via an interview with the subject approximately 2 months after the initial screening. It is implicitly assumed that these two different approaches for identifying SCARs are equivalent. It would be useful to demonstrate that using using the NHIRD data to identify SCARs in the prospective cohort gives the same results as the interview.

page 19 line 15: "which may have a huge impact on reducing the number of patients with allopurinol-induced SCARs in the population"

Page 18 - implication for clinical practice discussion
Discussion of cost-effectiveness of screening of the allele is warranted but the approach undertaken is somewhat limited. Results of cost-effectiveness analyses should be reported in the results section and the methods used described in the method section. The approach and results included in the discussion are rather simplistic and it is advised to either undertaken this in a more comprehensive manner or perhaps leave this for another study to focus on exclusively. For example, only two alternative strategies are compared - screening and universal use of febuxostat. While it is useful to highlight that a screening approach is likely to be less costly than universal use of febuxostat, this may not adequately provide insight into the cost-effectiveness of screening. For example, use of allopurinol without screening is not considered. I am not aware of the situation in Taiwan, but in many other countries the use of allopurinol without screening for HLA-B*58:01 is the standard practice, and universal use of febuxostat may not be considered cost-effective (and hence not a particularly good comparator).

Rather than describing this as a huge impact it may be more informative to the reader to provide some estimates of the impact in the population. For example, one could say (based on numbers in table 3) that screening approximately 110000 new users of allopurinol in Taiwan each year for HLA-B*58:01 may prevent approximately 330 cases of allopurinol-induced SCARs each year.

Additional Questions:
Please enter your name: Michael Sorich

Job Title: Associate professor of pharmacology

Institution: Flinders University

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

Fees for consulting?: No

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Reviewer: 4

Recommendation:

Comments:
BMJ.2015.025516

HLA-B*58:01 genotyping to prevent allopurinol-induced severe cutaneous adverse reactions: national prospective study

The authors report an historically controlled study looking at the incidence rate of allopurinol-induced severe cutaneous adverse reactions in a cohort of patients who are stratified for drug choice by HLA-B*58:01 genotyping. They show convincingly that avoiding use of allopurinol in people who tested positive for the HLA-B*58:01 allele. I have some comments on the presentation and statistical analysis.

1) The authors only followed participants for two months. Could they please provide stronger evidence and data supporting that adverse events are likely to occur within 2 months? (the current phrase is that "in general SCARs onset occurs within 2 months" which is not particularly convincing that all cases would have been detected). It would seem a weakness of the study not to have followed-up individuals for a longer time period, particularly seeing that the control group data are based on 3-monthly prescriptions.

2) The power calculation is written as if the comparison is being made between a known fixed value of 0.3% and a hypothesised value of 0.03% to be estimated within the sample. Given that the comparison is known and estimated with high precision this seems reasonable. However, the computed sample size does not agree with this (my sample size calculator using a normal approximation suggests that the stated sample size of 2169 would have 85.8% power (not the 99% stated). Could the authors fully justify and explain their calculation.

3) The statistical method the authors state has been used is a Fisher's Exact test. This is a two group test and requires data from both the screening cohort and the comparison group. It is not clear what data has been used for the comparison group in the analysis presented in the paper. However, in line with point 2) the comparison between the observed result in the collected cohort and the historical figure of 0.3% might be better based on a one sample Binomial test (to work out the probability that the see whether the observed incidence rate differs from the fixed value of 0.3%). My estimate of the associated P-value from this test is 0.0003 – thus similar to that reported by the authors.

4) It is important that the authors report the 95% confidence interval for the observed event rate in the cohort – (0% to 0.13%) as this gives an upper limit on the observed event rate.

Additional Questions:
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Reimbursement for attending a symposium?: No

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