tdelamothe@bmj.com

Subject: BMJ - Decision on Manuscript ID BMJ.2015.025321

Body: 23-Apr-2015

Dear Dr. Molnar,

Manuscript ID BMJ.2015.025321 entitled "Generic immunosuppression in solid organ transplantation: a systematic review and meta-analysis"

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 as we suggest in the report below from the manuscript meeting: we are provisionally offering acceptance but will make the final decision when we see the revised version.

Deadline: Because we are trying to facilitate timely publication of manuscripts submitted to BMJ, your revised manuscript should be submitted by one month from todays date. If it is not possible for you to submit your revision by this date, we may have to consider your paper as a new submission.

https://mc.manuscriptcentral.com/bmj?URL_MASK=23cb57b7bfbe410faa481a7984bd12bb

Yours sincerely,

Rebecca Burch, MD
Associate Editor, The BMJ
rburch@bmj.com,

** 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:

1. Deadline: Your revised manuscript should be returned within one month.

2. Online and print publication: All original research in The BMJ is published with open access. The full text online version of your article, if accepted after revision, will be the indexed citable version (full details are athttp://resources.bmj.com/bmj/about-bmj/the-bmjs-publishing-model), while the print and iPad BMJ will carry an abridged version of your article, usually a few weeks afterwards. This abridged version of the article is essentially an evidence abstract called BMJ pico, which we would like you to write using a template and then email it to papersadmin@bmj.com (there are more details below on how to write this using a template). Publication of research on bmj.com is definitive and is not simply interim "epublication ahead of print", so if you do not wish to abridge your article using BMJ pico, you will be able to opt for online only publication. Please let us know if you would prefer this option.
If/when your article is accepted we will invite you to submit a video abstract, lasting no longer than 4 minutes , and based on the information in your paper's BMJ pico evidence abstract. The content and focus of the video must relate directly to the study that has been accepted for publication by The BMJ, and

should not stray beyond the data.

3. Open access publication fee: The BMJ is committed to keeping research articles Open Access (with Creative Commons licences and deposit of the full text content in PubMedCentral as well as fully Open Access on bmj.com). To support this we are now asking all authors to pay an Open Access fee of £3000 on acceptance of their paper. If we accept your article we will ask you to pay the Open Access publication fee; we do have a waiver policy for authors who cannot pay. Consideration of your paper is not related to whether you can or cannot pay the fee (the editors will be unaware of this), and you need do nothing now.

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Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) and Committee in the space provided. You can use this space to document any changes you make to the original manuscript and to explain your responses. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

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'.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

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), Julie Morris (statistician), Jose Merino, Georg Roeggla, Tiago Villanueva, Rebecca Burch, Rubin Minhas (notes read in absence).

Decision: provisional acceptance

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:

*Editors felt that although this analysis is primarily confirmatory, this is a very relevant clinical issue. The concerns about generic medications seem to be stronger when the stakes are higher. Thus this is likely to be of interest to our general readers despite the somewhat specialist focus of these specific medications.

*We had no specific statistical concerns, although we did note that the results of the paper are limited by the small number of studies and the variable quality of the included studies.

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.

a. In your response to the reviewers and committee please provide, point by point, your replies to the comments made by the reviewers and the editors, and please explain how you have dealt with them in the paper. It may not be possible to respond in detail to all these points in the paper itself, so please do so in the box provided

b. If your article is accepted it will then be edited, proofed, and - after your approval - published on bmj.com with open access. This open access Online First article will not be a pre-print. It will represent the full, citable, publication of that article. The citation will be year, volume, elocator (a unique identifier for that article): eg BMJ 2008;337:a145 — and this is what will appear immediately in Medline, PubMed, and other bibliographical indexes. We will give this citation in print and online, and you will need to use it when you cite your article.

c. Please write an abridged version of the article for the print and iPad BMJ using the appropriate BMJ pico template for your study's design. Please be reassured that it doesn't take long to complete this. When your BMJ pico is ready please email it to papersadmin@bmjgroup.com.The templates for you to download are at
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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”

Abstract
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

Results

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/

summary statistics to clarify your message. Please include in the results section of your structured abstract (and, of course, in the article's results section) the following terms, as appropriate:

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:
- Sensitivity and specificity
- PPV and NPV (positive and negative predictive values)

For a systematic review and/or meta-analysis:
point estimates and confidence intervals for the main results

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

Discussion

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

Footnotes and statements

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

ID of ethics committee approval and name of the ethics committee/IRB; or a statement that approval was not required (see http://resources.bmj.com/bmj/authors/editorial-policies/guidelines) and a statement that participants gave informed consent before taking part

a statement that any identifiable patients have provided their signed consent to publication. Please submit, as a supplemental file, the signed BMJ patient consent form giving consent to publication in The BMJ of any information about identifiable individual patients. Publication of any personal information about a patient in The BMJ, for example in a case report or clinical photograph, will normally require the signed consent of the patient.

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signed patient consent form(s), if the article gives enough personal information about any patient(s): this sometimes occurs even in research papers - for example in a table giving demographic and clinical information about a small subgroup in a trial or observational study, or in quotes/tables in a qualitative study - (see http://resources.bmj.com/bmj/authors/editorial-policies/copy_of_patient-confidentiality)

a data sharing statement declaring what further information and data you are willing to make available, over and above the results reported in the paper. Suggested wording: "Data sharing: technical appendix, statistical code, and dataset [state whether any patient level data have been anonymised] are available at this repository or website OR from the corresponding author at ". If there are no such further data available, please use this wording: "Data sharing: no additional data available". For papers reporting the main results of trials of drugs or devices we require that the authors state, at a minimum, that the relevant anonymised patient level data are available on reasonable request from the authors
The BMJ has partnered with the Dryad Digital Repository datadryad.org to make open deposition easy and to allow direct linkage by doi from the dataset to The BMJ article and back - we encourage authors to use this option

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a statement describing the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication
assurance, in the cover letter, that a clinical trial funded by a pharmaceutical or other commercial company follows the guidelines on good publication practice (see http://resources.bmj.com/bmj/authors/article-submission/article-requirements)
inclusion in the list of contributors the name(s) any professional medical writer(s), specifying in the formal funding statement for the article who paid the writer. Writers and authors must have access to relevant data while writing articles.

Patient centred research
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:
did you involve patients/service users/carers/lay people in the design of this study? Please state whether you did, and give details (Methods section)
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)

REFEREE COMMENTS

Reviewer: 1

Recommendation:

Comments:
Molnar et al have performed the first systematic review on generic substitution of immunosuppressive drugs in patients following solid organ transplantation. The review was very thorough, and a large amount of information has been retrieved from the original studies. The methods used to do the review are state of the art. This review definitely gives a good overview of the studies that have been performed, and does add important information to the literature.
The authors conclude that the published studies on generic substitution in general are of poor quality. The vast majority of studies was of small sample size, insufficient study design or unclear regarding procedures of randomization. The review did not find that patients on generic immunosuppression suffered more often from acute rejection, nor from worse renal function.
In the discussion the authors argue that there is a need for well designed studies on generic substitution. It is questionable whether such studies are really needed. The registration of generic drugs is based on bio-equivalence. If the brand name drug and the generic drug are bio-equivalent the generic drug is registered, without requirement of proof that the two formulations result in similar clinical outcome. The registration authorities assume that two drugs present in blood in the same concentration will result in the same clinical outcome. This assumption, which I do support, has been in place for a long time, and has been used for many other generic formulations.

None of the studies in this systematic review was performed as part of a registration process. Some of the studies were performed on the initiative of generic drug companies, to show that their compound was not only bio-equivalent in healthy volunteers, but also in transplant recipients. For marketing purposes such studies may help in the battle with other generic companies. In other studies, often investigator driven, only clinical outcome was reported in cohorts of patients switched from one formulation to the other. These are typically underpowered studies, performed in low-risk patients.
I would argue that the transplant community should accept that for two drugs that are bio-equivalent there is no need to perform studies on clinical outcome. As long as patients receive proper instructions, and as long as the introduction of generic drugs is well coordinated the clinical outcome will be fine.
The message the authors convey is that although there is no proof that generic substitution is causing a problem, there also is no proof that it is safe. Their claim that well designed studies are needed is not correct. We do not need such studies. This claim will definitely be used by the companies producing brand name drugs to fuel the doubts the transplant community has regarding the introduction of generic immunosuppressive drugs. The authors mention that without the high-quality comparative trials the potential huge savings associated with the use of generics will not be fully realized. I would argue that the request for such studies (that are unlikely to be performed) hinders the introduction of generic drugs, and thus the cost savings.
And suppose we do want to perform prospective trials comparing brand name and generic immunosuppressive drugs, with a clinical primary endpoint. Will these studies need to be done in all the different organ transplants? And will we need such studies for all the different generic formulations on the market, or would one proof of concept trial be sufficient? Non-inferiority studies to compare the two formulations will need to have a very large sample size to be sufficiently powered. I do not think it is realistic to assume such studies will be done.
Overall I do think this systematic review is worth publishing, and I do think a high-ranked journal such as BMJ would be appropriate. However, in the discussion part of the manuscript it would be better to reconsider the plea for studies comparing clinical outcome in generic versus brand name drug.
Other comments:
- On page 5 the authors claim that in the UK generic substitution of tacrolimus and cyclosporine products was banned. To the best of my knowledge in the UK there is substantial generic substitution for tacrolimus already. Please clarify.
- The European Society for Organ Transplantation - guideline on generic substitution is missing (Transplant International 2011;24:1135–1141). Please add.
- On page 18 the authors claim that there is a general consensus that generic substitution should be performed in low-risk patients only. I do not think there is general consensus on this statement.
- Table 1b has “Neoral” in its title, but this should be “Prograf”.
- For a paper on this topic there should be extra attention for conflict of interest information. I would like to ask the authors if they can reconsider their statement that the in no conflict of interest for any of the authors.

Additional Questions:
Please enter your name: Teun van Gelder

Job Title: internist - nephrologist / clinical pharmacologist

Institution: Erasmus Medical Center Rotterdam - NL

Reimbursement for attending a symposium?: No

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: Sandoz, Roche, Novartis, Astellas, Siemens, Thermo-Fischer, Teva, Chiesi, Chugai: Consultant/Speaker received honoraria

Roche and Wyeth: Research Grant Support, study on transplant related diseases

Reviewer: 2

Recommendation:

Comments:
Review generic drugs for immunosuppression – Brian Godman – Division of Clinical Pharmacology, Karolinska Institute, Stockholm, Sweden and Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow, UK

A) General
Overall I enjoyed reading this very thought provoking paper in a topic area associated with appreciable controversy by both physicians and health authorities/ payers alike. The authors are to be congratulated on this – especially given the impressive number of initial papers identified (top of page 10) as well as subsequent studies included in the analysis (start of Discussion page 15). The methodology is comprehensive and explained very well - leading to good comments about the generally poor methodological quality of the RCTs (bottom of page 11) making conclusions difficult. As a result, the paper will add substantially to discussions about the use of generic medicines in immunosuppression. I also believe this is the first comprehensive meta-analysis in this field – but the authors know more about this.

I particularly like the conclusions giving guidance to authorities and clinicians worldwide for the future.

I would not alter very much within the paper, but may suggest the following to improve the introduction – especially given the very powerful last sentence on page 21 as well as lines 10 – 12 page 5 in the introduction.

A suggested order could be:
• Generic medicines are seen as essential to help maintain comprehensive and equitable health care especially within public healthcare systems given ever increasing pressure on resources - due for instance to changing demographics and the continued launch of new premium priced medicines to address areas of unmet need. The opportunity for savings is considerable (Ref 1 line 12 page 5) helped by high volume generics priced as low as 2% to 10% of pre-patent loss

prices in some countries in (i) Woerkom M, Piepenbrink H et al. Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications. Journal of comparative effectiveness research. 2012;1(6):527-38; (ii) Godman B, Wettermark B, Hoffmann M et al. Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance. Expert review of pharmacoeconomics & outcomes research. 2009;9(1):65-83; and (iii) Godman B, Wettermark B, van Woerkom M et al. Multiple policies to enhance prescribing efficiency for established medicines in Europe with a particular focus on demand-side measures: findings and future implications. Frontiers in pharmacology. 2014;5:106.

• Initiatives to enhance the prescribing and dispensing of generics versus originators include compulsory generic substitution, e.g. Sweden, substitution targets among pharmacies, e.g. France, and encouraging INN prescribing though education, e.g. UK, and lower co-payments in (i) Dylst P, Vulto A, Simoens S. Demand-side policies to encourage the use of generic medicines: an overview. Expert review of pharmacoeconomics & outcomes research. 2013;13(1):59-72 and (ii) Vogler S. The impact of pharmaceutical pricing and reimbursement policies on generics uptake: implementation of policy options on generics in 29 European countries — an overview. GaBI Journal. 2012;1(2):93-100. High voluntary INN prescribing the UK - average over 85% or more of all prescriptions – rising to 98-99% for high volume generics where limited concerns – is achieved starting with education in medical school and continuing post qualification in hospitals and the community - in (i) Ferner RE et al. Controversy over generic substitution. BMJ. 2010;340:c2548; (ii) Duerden MG, Hughes DA. Generic and therapeutic substitutions in the UK: are they a good thing? British journal of clinical pharmacology. 2010;70(3):335-41 and (iii) Godman B, Bishop I, Finlayson AE et al. Reforms and initiatives in Scotland in recent years to encourage the prescribing of generic drugs, their influence and implications for other countries. Expert review of pharmacoeconomics & outcomes research. 2013;13(4):469-82.

• Published studies have shown no apparent differences in outcomes between generic medicines and originators in for instance patients with CV diseases despite narrow therapeutic indexes of some of the medicines in (i) Kesselheim AS, Misono AS et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA. 2008;300(21):2514-26 and (ii) Corrao G, Soranna D, Merlino L, Mancia G. Similarity between generic and brand-name antihypertensive drugs for primary prevention of cardiovascular disease: evidence from a large population-based study. European journal of clinical investigation. 2014;44(10):933-9.

• The same was seen for generic and originator medicines to treat patients with epilepsy in Kesselheim AS, Stedman MR, Bubrick EJ et al. Seizure outcomes following the use of generic versus brand-name antiepileptic drugs: a systematic review and meta-analysis. Drugs. 2010;70(5):605-21. Having said this, there are concerns among the authorities in the UK with INN prescribing of certain medicines to treat patients with epilepsy – advocating continued prescribing of the originator (brand name prescribing) product as there is generic substitution is not currently allowed in the UK (i.e. if the physician prescribes the originator name when generics are available – the originator must be dispensed) – URL: https://www.gov.uk/drug-safety-update/antiepileptic-drugs-new-advice-on-switching-between-different-manufacturers-products-for-a-particular-drug.

• There is also controversy among the use of generic medicines in patients following solid organ transplantation (various references from 1 to 9 on page 5). This includes the UK where brand name (originator name) prescribing of for instance tacrolimus is endorsed by the authorities to minimise toxicity and graft rejection (not BANNED as stated on lines 48/ 49 page 5) and Denmark where generic substitution is not allowed.

• However – as mentioned at the bottom of page 5 – these recommendations from the authorities are not necessarily based on high quality evidence – with

the regulatory agencies arguing their methods of determining bioequivalence are reliable, etc. This includes tighter EMA/ Canadian regulations for cyclosporine (top of page 8). Then onto top of page 6 giving a good rationale and objective for the paper, etc.

B) Areas for potential consideration include:
• Page 7 – lines 22 – 27 – may be good initially to clarify that a 'brand name' is the originator name (if this is the case) as there are branded generics in for instance many European countries.
• Page 8 lines 46/ 47 – What are the main characteristics of the check list of Wells et al for those not totally familiar with this list?
• Page 9 lines 27 – 32. Need a reference for the Peto method as well as for the statement - 'this is the preferred estimate when cells contain 0 events'
• Page 10 – list of generics – what about INN generics as only branded generics documented?
• Page 11 – lines 32 to 34 – low number of patients included at 5. Maybe worth saying in the methodology that you did not exclude studies containing small number of patients as results were pooled, etc.
• Page 12 – lines 24/ 25 – may be better to say 'Tables 3A and 4A' as refer to the appendix
• Page 13 – line 27 - Can you recheck ref 44 as the authors in Sayyah et al 2007 in their paper documented no reports of major toxicity or of graft rejection and no need for dose adjustment related to Iminoral and concluded that renal transplant recipients maintained on Neoral can be safely and effectively converted to Iminoral on a 1:1 conversion ratio?
• Page 14 – lines 11 – 15 – need to explain why these two studies were included in the analysis if did not meet bioequivalence criteria (if this was the case) – see also next comment
• Page 15 lines 46 – 48 – was this all generic cyclosporines not meeting EMA/ Canadian bioequivalence standards? The same for tacrolimus and mycophenolate mofetil – yet despite this no significant differences in acute rejection rates for generic cyclosporine, tacrolimus or mycophenolate mofetil vs. originators.

C) Conclusion
In conclusion - this paper should be published.

Additional Questions:
Please enter your name: Brian Godman

Job Title: Professor

Institution: Starthclyde Institute of Pharmacy and Biomedical Sciences

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

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

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

END

Date Sent: 23-Apr-2015