Reviewer's report

Title: Inability to Achieve a Therapeutic Dose of Tacrolimus in a Pediatric Stem Cell Transplant Patient due to Generic Substitution

Version: 2  Date: 8 July 2014

Reviewer: Staffan Rosenborg

Reviewer's report:

Dear Authors,

Thank you for an interesting case report of GvHD during subtherapeutic tacrolimus exposure. This case report illustrates the many complexities and caveats of paediatric pharmacotherapy post ASCT. Due to several unclarities, I’m not convinced that one of these caveats is the use of generic tacrolimus. However, one of these caveats may be to involve too many different people and different pharmacies in the compounding of ex tempore preparations of narrow therapeutic index (NTI) drugs.

MAJOR COMPULSORY REVISIONS

1) General: The drop in tacrolimus concentrations after switching to generic tacrolimus coincides with a profound decrease in the dose of voriconazole, a known inhibitor of tacrolimus metabolism. The rise in tacrolimus concentrations after switching back to originator tacrolimus coincides with a dose increase in voriconazole. Please explain why you still feel that the conversion to brand tacrolimus was the explanation to the rise in tacrolimus levels and resolution of GvHD. You discuss different factors potentially influencing the tacrolimus levels on pages 6 and 7, yet reject these explanations because your emotions told you otherwise (Discussion, page 9). Please use scientifically sound arguments instead.

2) General: The generic tacrolimus formulation is not stated: which one was it or was it several?

3) Background: You’re wrong regarding the definition of bioequivalence. Please read, contemplate, and re-read and re-contemplate the FDA guidelines and correct the manuscript accordingly. This isn’t easy.

4) Case Presentation: The oral suspension was prepared from capsules by different pharmacies and different pharmacists. You claim the solvents were the same, but you don’t state which ones. “Syrup” could be anything sweet and “oral suspending vehicle” could mean virtually anything liquid. Has the stability of the resulting oral suspension been tested or what is the base for claiming 56 days stability? Why don’t you use granules for oral suspension (Modigraf®)?

5) The Figure is quite confusing; take away the half circle symbols from the therapeutic window limits, they just mess up the picture. Please align the Y-axes: they’re slightly unaligned making it hard to understand what TAC and VCZ doses
are given exactly when. Consider stating both tacrolimus brand and route of administration throughout all panels (preferably by shaded bands or other kind of vertical demarcation) instead of stating brands in the uppermost panels and route of administration in the other panels. Consider drawing both TAC and VCZ doses in the same graph. Consider describing the development of GvHD (Did it disappear on day 60 or when? Did it reappear during periods of subtherapeutic tacrolimus levels on originator tacrolimus?). The VCZ doses given in the Figure is not concordant with those stated in the text (the dose before generic TAC seems to have been somewhere around 17-18 mg/kg/day and not 12 mg/kg b.i.d. as stated).

MINOR ESSENTIAL REVISIONS

6) Please explain what Table 1 adds and consider revising it to meet this purpose.

7) Case presentation: How do you define appropriate times for trough levels? How much of the zigzag pattern can be explained by either non-steady state or irregular sampling?

8) Discussion and References: Please explain the relevance of the in vitro study (ref 15) to the present case; are any of the investigated tacrolimus preparations available in the US or are they even tested for bioequivalence? The FDA defines bioequivalence as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." I doubt that this can be shown for some of the preparations described in the reference (which, in addition, may very well be biased as it is performed and funded by Astellas). Authorized generic tacrolimus preparations in the US should be bioequivalence tested. Such preparations would most likely need to have similar dissolution properties as originator tacrolimus in order for bioequivalence to be demonstrated. The danger of using tacrolimus preparations that have not been tested for bioequivalence has been described by e.g. Noceti et al [Ther Drug Monit 2011;33(P246):545]. Thus I doubt the relevance of this study for the present case report in its US setting.

9) Discussion and References: Please explain the relevance of the rat study cited (ref 22).

10) Conclusion: What do you mean by bioequivalence studies done in animals? Are you referring to that rat study (ref 22) again or does the FDA accept BE studies made in animals???

DISCRETIONARY REVISIONS

1) General: Prograf® is a brand name and should be written with capital P.

2) General: I note that you consequently claim tacrolimus to have been measured in serum. Don't you mean whole blood? Otherwise you'll need to describe the method thoroughly and explain why the levels measured are the same as usual whole blood levels. It would be interesting to know where the tacrolimus levels were measured and by which method. Was it the same lab and
analytical method or were different TDM services involved?

3) Abstract: Here you write allogeneic bone marrow transplantation, but otherwise you write stem cell transplantation (also allogeneic, I suppose). Please check and stick to the therapy actually given.

4) Discussion and References: You may consider including a paper on a prospective study of conversion to generic tacrolimus in stable kidney transplant recipients (Clin Kidney J. 2014;7(2):151-5) in addition to your references to retrospective studies and the PK study by Rita Alloway et al where the patients were switched back to their previous brand after study completion.

5) I’ll leave to the Editor to decide upon the compliance with editorial rules of manuscript format. I didn’t have access to your ticked CARE Checklist and haven’t scrutinized adherence to the CARE statement. However, the CARE statement requires “case report” to be part of the manuscript title. I’ll leave to the Editor to decide whether the BMC Pharmacol Toxicol considers this requirement to be filled by the section heading. I would, however, suggest that you check editorial formalities once again.

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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I do not have any financial or immaterial competing interests.

However, I am a member of the Stockholm County Council Therapeutic Drug Expert Panel for Renal Medicine and am the first author of a prospective switch study to generic tacrolimus in (adult) kidney transplant patients. Thus I am pro the use of generic immunosuppressants but strongly believes that these, as all drugs, should be used rationally and consequently (i.e. keeping each patient to a specific brand and monitoring every further switch).

This also means that I have read and contemplated quite a lot about bioequivalence and these authors have obviously not.