Reviewer's report

Title: Effect of vancomycin serum trough levels on outcomes in patients with nosocomial pneumonia due to Staphylococcus aureus: a retrospective, post hoc, subgroup analysis of the Phase 3 ATTAIN studies

Version: 2 Date: 13 September 2013

Reviewer: Daniel Kett

Reviewer's report:

This retrospective analysis examines the clinical outcomes of patients with hospital-acquired pneumonia (HAP) due to Staphylococcus aureus treated with vancomycin in patients enrolled in the ATTAIN trials. The study investigates the relationship between vancomycin serum trough levels and patient outcome.

The ATTAIN studies were designed to assess the clinical efficacy and safety of telavancin compared with vancomycin in the treatment of HAP due to gram-positive organisms, with a focus on infections due to MRSA. For patients with suspected or documented gram-negative infection, aztreonam use was permitted by protocol.

Their data suggest that higher vancomycin trough levels do not result in improved clinical response but likely increase the incidence of nephrotoxicity. As the authors correctly point out, this is an important topic. While the recent guidelines support a vancomycin trough level of 15–20 µg/mL, I am not aware of any prospective data that demonstrates improved clinical outcome when prescribing vancomycin aimed at achieving these levels or the alternate AUC/MIC targets. As the authors acknowledge, the results of the ZEPHyR trial suggest that higher trough levels of vancomycin were associated with lower cure rates in patients found to have MRSA pneumonia.

However, I believe there are major flaws in the analysis which severely limit interpretation of the results.

Major Compulsory Revisions:

1. This study is underpowered to draw meaningful conclusions.
2. I believe the authors incorrectly chose the population for this analysis with the primary group for analysis being HAP patients with MRSA. While the pharmacokinetic question related to the effectiveness of vancomycin trough levels on outcomes in Staph. aureus pneumonia should be independent of resistance, most guidelines recommend and routinely done in clinical practice, clinicians often switch to an anti-staphylococcal penicillin/cephalosporin when MSSA is recovered (outside of the highly penicillin allergic patients or patient intolerant to vancomycin). While in the ATTAIN trials this was done infrequently, inclusion of MSSA patients in the primary analysis again would seem
inappropriate and any conclusions uninformative. Unfortunately, limiting the analysis to the 76 HAP patients with MRSA would further underpowers the study.

3. As there is an extensive body of literature focusing on the impact of effective initial antibiotics on outcome, I think the analysis should focus on the early vancomycin trough levels within the first 3-4 days and not the median vancomycin trough level. Averaging early and late trough levels (especially those after day 7, often when then infection should be clinically improved) is not informative.

In the ATTAIN trial, vancomycin was prescribed as a fixed initial dose at 1 g q 12 hours. This does not conform to the current weight based dosing recommended by most guidelines and often done in clinical practice. While the data is not presented, I would suspect this will result in lower early vancomycin trough levels. While the manuscript states that vancomycin dosing could be monitored and adjusted for weight and/or renal function according to site specific standard procedures (while maintaining study blind), not having a set protocol for the ATTAIN study further limits interpretation of the data.

Minor Compulsory Revisions:

1. The authors do not describe how they determined if a vancomycin level was labeled a trough versus random level.

2. Including patients with acute renal injury and/or previous vancomycin exposure further weakens the primary analysis.

3. The study used a non-standard definition of renal adverse events which included chronic renal failure. If possible, reanalyzing the data using the more standard definition of nephrotoxicity (such as the RIFLE or AKIN criteria) would be more informative.

Recognizing these limitations, I believe this is an important topic which deserves consideration for publication. For the foreseeable future, secondary analysis from large clinical trials (such as ATTAIN and ZEPHyR) is the only likely source of data related to vancomycin trough levels and their influence on clinical outcome in pneumonia patients.

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:
In the past five years I have received research support, served as a consultant to, and was on the speakers bureau of Pfizer, Astellas, and GlaxoSmithKline.