Author's response to reviews

Title: A randomized trial of tigecycline versus ampicillin-sulbactam or amoxicillin-clavulanate for the treatment of complicated skin and skin structure infections

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Author's response to reviews: see over
July 12, 2012

Dear Dr. Sakoulas:

Re: MS: 3767286146296438

Thank you for the peer review comments on this manuscript. We have addressed the reviewer comments, revised the manuscript accordingly, and have responded to each comment.

Please let me know if you need anything further. Thank you again for considering this manuscript for publication in your journal.

Kind regards,

Peter Matthews
Reviewer: Warren Rose
Reviewer’s report:

Major Compulsory Revisions

1. Vancomycin could be added to the comparator regimen if MRSA was suspected or confirmed. This agent could be dose adjusted per local guidelines as described. Some universal guideline should have been applied given what is recommended for use and monitoring of vancomycin (Rybak et al Am J Health Syst Pharm. 2009 Jan 1;66(1):82-98). A general description of local guidelines should be given.

- The reviewer should be aware that the guidelines published by Rybak in 2009 occurred after completion of study enrolment. The study was conducted at 77 centers and local guidelines were not collected as part of the study. Vancomycin dosing adjustment based on age, kidney function, and therapeutic monitoring of serum concentrations was left to the expertise and standard of care provided by the individual investigators.

2. Subjects could not receive more than 24 hours of prior antibiotic therapy, unless they were a failure on prior antibiotic therapy. What was considered prior antibiotic therapy failure?

- Receipt of prior antibiotics for ≥3 days prior to first dose of study drug with no improvement in signs/symptoms of infection (a culture was also required to ensure that this group did not include late responders and allowed identification of resistant pathogens); added to manuscript p7

3. Did any patients have bacteremia as a result of cSSSI. A low percentage of patients with cSSTI have concomitant bacteremia (<5%), but this would be relevant to know if this occurred in this study since tigecycline achieves very low serum concentrations. If so, it would be prudent to exclude these patients.

- Information on subjects with baseline bacteremia was provided in the manuscript on page 11. The protocol did not specify removal of subjects with bacteremia, therefore this would not be appropriate.

Minor Essential Revisions

1. MIC testing was done by broth microdilution and Kirby-Bauer. Later the authors present MIC90 values of 1 mg/L for vancomycin. Kirby-Bauer is no longer an acceptable method for vancomycin testing with S. aureus. Please confirm if this MIC90 number represents that found with broth microdilution.

- Kirby-Bauer was done in addition to broth microdilution for tigecycline only. All other antibiotics including vancomycin had MIC determined by broth microdilution; manuscript revised p 9.

2. Was there a tertiary reviewer for clinical efficacy determination or was this determined by the treating physician?

- The investigator evaluated the subject's clinical response.

Discretionary Revisions

1. Having a vancomycin MIC90 of 1 does not constitute creep as the authors indicate. Consider revising this statement.

- MIC creep is not associated with a specific MIC but is defined as rising MIC of vancomycin among susceptible Staphylococcus aureus (Dhand and Sakoulas F1000 Medical Reports, 2012). 97% of S. aureus isolates in this global study had MIC ≥1 consistent with observations describing this phenomenon. The manuscript was altered to clarify that 97% had MIC≥1 on page 12 and page 15.
2. The discussion states that in previous studies, all-cause mortality has been observed in the tigecycline clinical program. It would be useful to elaborate on this to include what groups have increased mortality.

- All-cause mortality has been observed in the clinical program overall but with substantial differences among evaluated infection types. Hospital-acquired pneumonia, in particular subjects with ventilator associated pneumonia, had the highest mortality rates. All-cause mortality was not the topic of the trial and the complicated nature of the topic preclude appropriate elaboration of the topic within the context of this manuscript. Information on all-cause mortality is the topic of other concurrent publications.
Reviewer: RAVINA KULLAR
Reviewer’s report:

Major Compulsory Revisions:
1. Introduction – overall, the introduction section is very abbreviated. The authors could expand this by discussing in further detail about CA-MRSA, especially since the authors choose to distinguish between HA-MRSA and CA-MRSA via mec typing. What does the current literature state about SCCmec IV vs. SCCmec II and CA-MRSA vs. HA-MRSA? Would also expand on the coverage of tigecycline. What do the IDSA guidelines state about the role of tigecycline for MRSA infections?

• With respect to the reviewer, the purpose of the trial was compare the efficacy of tigecycline with that of the comparator regimen. The introduction conveys the need for agents that can be used against what can be a diverse bacterial etiology and briefly introduces tigecycline and prior studies in cSSSI. We agree with the reviewer that information on the coverage of tigecycline would be useful information to the reader and we have added to the introduction.

• The molecular profile of MRSA and the efficacy of tigecycline against MRSA with different molecular profiles was not a major objective of the trial. The information in the paper on CA-MRSA was provided for the readers’ information only. Discussion of this information would detract from the stated purposes of the trial and would not provide meaningful information on this topic that has been provided in other publications.

• The contents and recommendations of the MRSA guidelines are not appropriate for the introduction however information on tigecycline in various guidelines have been added to the discussion (p15-17).

2. Methods (under “Subjects”; 1st paragraph) – authors need to clarify what is meant by “complicated underlying disease.”

• Clarified on p6: diabetes mellitus, peripheral vascular disease, peripheral neuropathy, or venous insufficiency

3. Methods (under “Efficacy and Safety Evaluations”; 2nd paragraph) – was any other molecular testing performed? PVL production? Lineage (USA300, etc)?

• No.

4. Methods – General comment. Did the authors look at clonal identity for the MRSA strains, especially those collected in the same year. Even though the authors selected unique patients, this does not mean there has not been dissemination of the same clone.

• No.

5. Results (under “Patient Characteristics”; 1st paragraph). What was the median (IQR) duration of therapy the comparator group received vancomycin therapy? What was the median initial vancomycin trough concentration?

• The median duration of vancomycin therapy was 5 days. This represent the median dosing for all subjects given vancomycin and does not represent the median length of therapy for subjects with MRSA. Vancomycin concentrations were not collected.

6. Results – General comment. Did any patients in the tigecycline group receive combination therapy? If so, what combination?

• The protocol did not permit concomitant therapy in the tigecycline group.

7. Table 1 - there was no measurement of severity of illness such as APACHE II scoring.
8. Table 1 – what prior antibiotics that patients failed on were these patients on?

- Per protocol, subjects could fail on any prior antibiotic regimen except tigecycline, vancomycin, or the aminopenicillin/β-lactamase inhibitor. No information was added to the manuscript.

9. Results (under “Safety and Tolerability”; 1st paragraph). It is concerning that patients in the tigecycline group experienced more nausea, vomiting, and diarrhea. What is the breakdown of these adverse events by pathogen?

- Gastrointestinal intolerability is a class effect well known to the tetracyclines and tigecycline. It is not related to the specific pathogen being treated.

10. Discussion – overall, the discussion is brief. Can be expanded by discussing about the limitations of other therapeutic agents approved for cSSSIs and MRSA infections. What makes tigecycline an ideal agent to choose above other agents for cSSSI? Appears to be no discussion of this.

- With respect to the reviewer, the review of the benefits or limitations of agents used in the treatment of cSSSI is the purpose of treatment guidelines. The purpose of the trial was compare the efficacy of tigecycline with that of the comparator regimen and the results of the trial can be used to inform future guidelines.
- The authors have suggested on page 15 that tigecycline may be useful as empiric therapy for hospitalized subjects that require a broad spectrum antibiotic as well as activity against MRSA. In addition we have added information on where tigecycline therapy may be appropriate and added information on tigecycline in currently published guidelines as requested above

Minor Essential Revisions:

1. Methods (under “Subjects”, 2nd paragraph) – how did authors handle patients with spontaneous drainage? Define uncomplicated skin infections.

- Subjects with spontaneous drainage had to meet the criteria of having a major abscess and therefore were not differentiated from other subjects with major abscess without spontaneous drainage.
- Added uncomplicated descriptor to page 6 (e.g., simple abscesses, folliculitis, impetiginous lesions, furunculosis, or superficial cellulitis)