Title: Daptomycin Therapy for Osteomyelitis: A Retrospective Study

Authors:

Jason C Gallagher (jason.gallagher@temple.edu)
Jennifer A Huntington (jennifer.huntington@cubist.com)
Darren Culshaw (darren.culshaw@cubist.com)
Scott McConnell (scott.mcconnell@cubist.com)
Minjung Yoon (min.yoon@cubist.com)
Elie Berbari (berbari.elie@mayo.edu)

Version: 2 Date: 22 March 2012

Author's response to reviews: see over
Dear Editor:

We would like to resubmit our manuscript “Daptomycin Therapy for Osteomyelitis: A Retrospective Study”, which summarizes the available information on the clinical outcome and safety of patients with non-hardware associated osteomyelitis treated with daptomycin. The following pages address how we have responded to and incorporated the comments suggested by the three initial reviewers. We would like you to consider publication of this manuscript in *BMC Infectious Diseases*.

All of the authors of this manuscript have fulfilled the criteria for authorship, reviewed and approved the paper, and attest to the integrity of the work submitted.

Please address all correspondence to me at the contact information noted below.

Thank you very much for your attention to this matter.

Sincerely,

Jennifer A. Huntington, Pharm.D.
Cubist Pharmaceuticals, Inc
65 Hayden Avenue, Lexington, MA 02421
Phone: 781-860-8751
Fax: 781-240-3075
jennifer.huntington@cubist.com
General Comments

1. In addition to the comments from the reviewers, please clarify whether any ethical approval or permissions were required to access the database in your study and use the information for research purposes. Please include a statement of any permissions required in the Methods section or state that no ethical approval was required if none was needed.
   - Response: A sentence stating that the study was approved by the investigational review board of the study centres was added to the methods section.

2. Please also ensure that your revised manuscript conforms to the journal style
   - Response: Files have been appropriately reformatted according to the “BMC-series medical journals - authors' checklist for manuscript formatting”. In addition, the figures have been reformatted and cropped into PDF documents.

Referee #1

Reviewer: Matthew Leibowitz

Reviewer's report:

1. No Major Compulsory Revisions
   - Response: No need to address.

2. No Minor Essential Revisions
   - Response: No need to address.

3. No Discretionary Revisions
   - Response: No need to address.
Referee #2

Reviewer: RAVINA KULLAR

Reviewer's report:

Major Compulsory Revisions

1. Page 5-“To determine the persistence of clinical success…” Investigators should have a set follow-up end point. Difficult to determine what the follow-up period actually is and how one would interpret this… anywhere from 1-2 years?
   - Response: Although untraditional as a follow-up visit, all patients had their medical records monitored for any indication of a return visit related to their osteomyelitis for one year as part of the follow-up data collection for the study.

2. Page 6-“During that time period, the longest assessment…” Having a variable follow-up period is not beneficial to the clinician. The authors should have a predefined follow-up period rather than having a range of follow-up period as this means nothing to the reader in terms of assessment.
   - Response: We have corrected the sentence to only state the 35 days is the median value. The results reflect the standard of care at the institutions involved in the study. The information provided should allow the clinician to assess if the results apply to their clinical practice. The retrospective, non-interventional nature is a limitation which has been addressed in the discussion.

3. Page 7 and Figure 2-“No difference in the failure rate between daptomycin dosing groups was identified.” Since the sample size in the patients receiving < 6 mg/kg (n=24) vs. > 6 mg/kg (n=47) was so different, the results should be interpreted cautiously. Additionally, in performing a Kaplan Meier analysis, the smaller the sample size is, the longer the intervals will be, raising the question of whether the assumption of a constant survival probability within each interval is appropriate.
   - Response: We agree that due to the sample size and the amount of censored data, we should use the analysis with caution. We have modified the text to address this concern.

4. Discussion-would include small sample size as a limitation as this could have played a role in the results from the Kaplan Meier analysis.
   - Response: We have modified the text to address concern.

Minor Essential Revisions

1. Page 4-“Recent data suggest that…” The references the authors provide for this are older as there have been more recent publications that have determined this. (Moore CL, et al. AAC 2011 Oct; 55(10); Kullar R, et al. CID 2011 Apr; 52(8)).
   - Response: We have incorporated Dr. Kullar’s publication as suggested.

2. Background-Has there been any in vitro or in vivo data published on daptomycin in osteomyelitis models? If so, may strengthen background.
   - Response: We have added data from early in vivo animal and clinical experiences to the background.

3. Page 4-Reword aims as the current wording sounds awkward
   - Response: Aims have been reworded.
4. **Results**—did all patients have normal renal function? Any patients have ARF or were on HD?
   o Response: Table 2 has been updated to reflect the numbers of patients with severe renal failure (CrCl <30 mL/min) or those on dialysis at the time of initiation of daptomycin therapy.

5. **Results**—would be beneficial to have severity score (APACHE-II, Charlson score, etc.) to assess how sick these patients were
   o Response: We recognize the utility of these data. Unfortunately this information was not collected as part of the case report form for the patients in this study, so this data cannot be reported. The Charlson score/index measures comorbidities, and some of these data were collected and reported in the manuscript. APACHE II scores are not available, and are of questionable relevance since these patients were largely not critically ill.

6. **Page 7**—“Thirty-six adverse events…” There was no reference to adverse events in the methods section. What was the definition of “possibly related to daptomycin”, etc?
   o Response: Information on the collection of adverse events, including definitions of the relationship categories, was added to the methods section as:
     “The causal relationship between daptomycin treatment and the adverse event was described by the investigator as either not related (an adverse event with a temporal relationship to the drug administered that makes a causal relationship improbable, and/or for which other drugs or underlying or concurrent disease provide a plausible explanation) or possibly-related (a plausible temporal relationship to the drug administered, but for which other causative factor(s) could account for the event and where improvements on dechallenge or dose reduction may or may not have been observed).”

7. **Table 2**—What was the definition of “Blood CPK Increase” – there is nothing in the methods section as to what is considered an increase in CPK. How many patients had a baseline, follow-up and end-of-therapy CPK level drawn?
   o Response: Investigators were trained on all aspects of regulatory requirements for reporting adverse events. As part of this training the approved labeling for daptomycin, including data on CPK monitoring and adverse events, was reviewed. The investigators applied all clinical data from the patient record to assess if an adverse event had occurred up to 30 days after completing therapy; no definition for CPK increase was provided. The assessment of CPK values was based on the standard of care at the institution. Additional data on CPK assessment has been added to the safety section.
Referee #3

Reviewer: Abhay Dhand

Reviewer's report:
This study addresses an important knowledge gap in the long-term use of daptomycin for chronic infections like osteomyelitis and measures clinical and safety outcomes.

Major limitations regarding clinical outcomes:

1. **Diagnosis** - there is a lack of uniformity in making/confirming a diagnosis of osteomyelitis. Only 56/71 pts had radiologically confirmed osteo. While culture data was available from at least 52 pts., it was used in only 29 pts. to confirm the diagnosis of osteo.
   - Response: This study collected data based on the standard of care practiced at each institution, as such diagnostic procedures and surgical interventions were uncontrolled. No specific diagnostic test was required to confirm the diagnosis of osteomyelitis as part of this study. Tests/factors that lead the investigator to a diagnosis of osteomyelitis were only collected in the case report form if they were specifically mentioned in the patient chart. We have clarified that the 29 patients that used cultures for diagnosis of osteomyelitis were primarily from bone.

2. **Clinical outcome**: unclear what the relevance of clinical outcome in pts. With either gram negative infection, culture negative infection and/or in pts. Where osteo was confirmed neither radiologically nor microbiologically.
   - Response: We have addressed this comment by including a subgroup analysis of patient with these characteristics: “A subgroup analysis of 63 patients with confirmed osteomyelitis (radiologic evidence and/or bone culture), 52 patients with Gram-positive pathogens and 28 patients receiving daptomycin monotherapy showed success rates of 94% (CI - 85%, 98%), 96% (CI - 87%, 99%), and 96% (CI - 82%, 99%), respectively. For the 18 patients meeting all 3 of these characteristics, the overall success rate was 94% (CI - 73%, 99%)”.

3. **Only 28/71 (39%) pts. were treated with daptomycin alone, so the significance or the role of a broad spectrum concomitant antibiotic in curing osteo. Becomes unclear.**
   - Response: See above response to comment #2.

4. **Definition of clinical response**: one of the definitions (infection cleared with a negative culture result) will be virtually impossible in these patients.
   - Response: The definition of outcome in the registry took a general approach that could be applied to various infections. We agree that the qualifiers in the definitions do not often apply to osteomyelitis patients; even the use of “cured” is controversial. We have added additional data on the parameters the investigator used to assess outcome in the results section.

5. **Lack of uniform/standard definitions in this study leads to a result where daptomycin dosage of 4 mg/kg vs. higher does not affect the rate of clinical failure. This could be potentially misleading in future treatment of pts. with serious MRSA infections.**
Response: The discussion section which reviews other data related to dose, has been written to put these results in perspective.

6. This study can be more clinically relevant if the clinical outcome data is limited to patients where the diagnosis of osteomyelitis has been uniformly confirmed and where microbiological data shows susceptibility of the organism to daptomycin and other confounding factors like concomitant antibiotics are excluded. This may decrease the total number of patients, but the results will be clinically relevant and meaningful.

Response: See above response to comment #2.