

## Reply to comment “Comment on Jugun et al.: The safety and efficacy of high-dose daptomycin combined with rifampicin for the treatment of Gram-positive osteoarticular infections” by Lu et al.

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Dear Prof. Pecina,

We thank you for the opportunity to answer the letter commenting on our published article entitled “The safety and efficacy of high-dose daptomycin combined with rifampicin for the treatment of Gram-positive osteoarticular infections”.

The colleagues Lu, Zha and Wang have read our paper and highlight some remarks (or opinions as they call it), which we find pertinent and answer them with pleasure.

1. We are aware of the small sample size of 16 patients and this is acknowledged in the manuscript [1]. This is not new. However, Lu and colleagues need to bear in mind that our study addressed the question of the clinical feasibility and tolerance of high-dose daptomycin (8 mg/kg/day) combined with rifampicin, another drug used in orthopaedic surgery with a potentially important side-effect profile. As a general principle, studies targeting the outcome of interventions usually need sample sizes beyond 50 cases in each randomisation arm, as Lu and colleagues correctly remark. These are usually phase III trials or other investigations regarding cure or failure rates.  
In contrast, tolerability studies in humans, e.g. many phase II trials, are appropriate with a much lower sample size and may be performed within a single centre such as in our study. Therefore, it is not surprising that the local Institutional Review Board and Swissmedic (The Swiss “FDA”) approved our small sample size.
2. Lu et al. ask why we chose daptomycin 8 mg/kg/day combined with rifampicin. Although we explained this in the publication, two reasons predominated. First, daptomycin is under evaluation worldwide for higher doses than the usual 6 mg/kg/day for all types of infections.

Theoretical concerns discourage using higher doses, even when a higher dosage could have advantages. Thus, we chose 8 mg as a first step for the investigation. A submission involving a higher jump, e.g. directly from 6 mg/kg to 10 mg/kg, was likely to have been rejected by the Swiss Federal authorities. Second, a combination with rifampicin (or rifampin) is a well-established standard antibiotic regimen for staphylococcal implant infections, the hallmark of orthopaedic infections.

3. Lu et al. regretted the absence of clinical functional recovery data post infection treatment. They would have been correct if the main investigation of our study had been the Therapeutical approach. In our article, we concentrated on the tolerability and safety of a particularly promising antibiotic combination at high doses. Such a manuscript would have been complicated and too long if we had added functional outcomes. Antimicrobial drugs have a range of adverse events, including fatal ones. In most cases however, adverse events usually subside within a few weeks, with absence of long-term sequelae. None of our study patients had antibiotic therapy related sequelae, and any functional impairment depended on the anatomical and orthopaedic conditions predating their infection.

We thank again Lu et al. for their thorough reading of our article and their collegial remarks. We remain open for further questions.

Yours most sincerely,

I. Uçkay, MD, and Prof. P. Hoffmeyer, MD

### Reference

1. Jugun K, Vaudaux P, Garbino J, Pagani L, Hoffmeyer P, Lew D, Uçkay I (2013) The safety and efficacy of high-dose daptomycin combined with rifampicin for the treatment of Gram-positive osteoarticular infections. *Int Orthop* 37:1375–1380. doi:10.1007/s00264-013-1856-y

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