Reviewer’s report

Title: Daptomycin in experimental murine pneumococcal meningitis

Version: 1 Date: 26 February 2009

Reviewer: Christian Østergaard

Reviewer’s report:

The study "Daptomycin in experimental murine pneumococcal meningitis" by Mook-Kanamori et al. evaluates the treatment efficacy of daptomycin compared to treatment with vancomycin and to no antibiotic therapy, when all treatment regimens were combined with adjunctive dexamethasone therapy.

Antibiotic concentrations in serum were studied, and the primary endpoint parameter in this newly established murine pneumococcal meningitis model was the CSF bactericidal effect. Moreover, degree of infection was evaluated by bioluminescence imaging, and histological evaluation of brains was performed to document infection as well as degree and pattern of brain damage.

The study showed that antibiotic treatment resulted in a significant CSF bacterial killing when compared to untreated controls and that treatment with daptomycin was comparable or even slightly better than treatment with vancomycin. No significant difference in degree of brain damage was observed between the 3 experimental groups.

The study explores a relevant clinical situation, namely antibiotic efficacy during dexamethasone therapy – the recommended therapy of bacterial meningitis in industrialised countries - and therefore provides new important knowledge.

The murine meningitis model was successfully established demonstrating typical histopathological findings of meningitis (e.g. meningeal inflammation, vasculitis and hemorrhage, necrosis and abscess formation and neural apoptosis). All methods were relevant and well executed, though CSF WBC concentrations were compromised by blood contamination due to traumatic CSF tapping (how often? Could be adjusted, if a corresponding blood samples were obtained) and that technical problems resulted in bioluminescence imaging of only 73% of animals. In addition, this method was of limited value in the present study; despite bioluminescence imaging is a highly relevant method for studying the pathogenesis and pathophysiology of bacterial meningitis and therefore might be of relevance in future experimental studies from this group.

Pharmacokinetic analysis would have been more complete by studying CSF antibiotic concentration and not only serum concentration, because adjunctive therapy with dexamethasone potentially could reduce CSF antibiotic penetration.

Treatment with daptomycin (without concomitantly dexamethasone therapy) was previously shown to cause less brain damage than conventional antibiotic therapy. Moreover, treatment with dexamethasone, when combined with
ceftriaxone, caused increased hippocampal injury than treatment with ceftriaxone alone. Therefore, the present study would have been more interesting, if experimental groups not given dexamethasone also were included.

Minor Essential Revisions.

Background, 2. paragraph. Please add the results of previous experimental meningitis studies with daptomycin to clarify to relevance of the present study.

Methods, line 64. “Serotype 3 is one of the most common pneumococcal serotypes” will be more correct.

Methods, line 89. 3 x 10e4 CFU of bacteria.

Methods, line 89, please give doses of ketamine and xylazine.

Methods, line 98. Were mice reanesthetized with ketamine and xylazine?

Methods, line 100-2. Since lower detection limit was 20 CFU/mL, please indicate that 50 µL of undiluted CSF also were plated.

Figure 1. Labelling seems not to be correct. DX = control? Control = DP?

Figure 3. Confidence intervals are overlapping and therefore difficult to evaluate. Please separate, if possible.

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 declare that I have no competing interests