



# The clinical efficacy of lefamulin in the treatment of elderly patients with community-acquired bacterial pneumonia

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Community-acquired bacterial pneumonia (CABP) remains a common cause of elderly patients requiring hospitalization and it can also be associated with significant morbidity and mortality (1-3). Common causative pathogens of CABP include typical pathogens—*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and the atypical pathogens—*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*. Appropriate antibiotics are the key of successful management of elderly patients with CABP (2), however, the emergence of antimicrobial resistance among these respiratory pathogens limits the choice of antibiotic and could negatively impact the outcomes of the elderly patients with CABP.

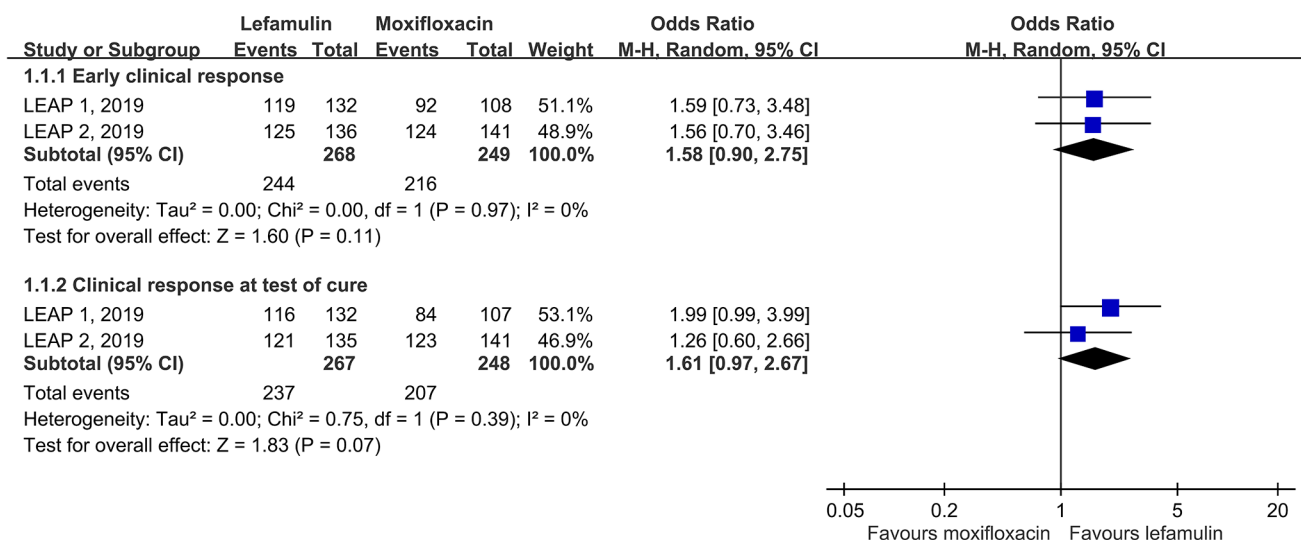
Fortunately, recent development of a novel antibiotic—lefamulin, the first systemic pleuromutilin antibiotic, is active against the most common CABP-causing pathogens, including both typical and atypical pathogens and can provide us a therapeutic alternative in this clinical entity (4). In addition to *in vitro* studies (5,6), two phase III studies—Lefamulin Evaluation Against Pneumonia (LEAP) 1 trial (7) and LEAP 2 trial (8) have reported the clinical efficacy and safety profile of lefamulin for treating CABP. However, the usefulness of lefamulin in the elderly patients remains unclear. Therefore, we extracted the results of LEAP 1 and 2 trials (7,8) for the elderly patients and did a meta-analysis to investigate the clinical efficacy of lefamulin in the treatment of elderly patients with CABP.

Both LEAP 1 and 2 trials were phase III, randomized, double-blind, double-dummy, multicenter, multinational studies (7,8). LEAP 1 trial (7) compared the usefulness

of iv-to-oral lefamulin and moxifloxacin ± linezolid in the treatment of adult patients with CABP at Pneumonia Outcomes Research Team (PORT) risk class ≥ III. LEAP 2 trial compared the clinical efficacy of oral lefamulin and oral moxifloxacin for treating the adult patients with CABP at PORT risk class II, III or IV (8). The primary outcomes included early clinical response at 96±24 hours after first study drug dose in the intent-to-treat (ITT) population and investigator assessment of clinical response at test of cure (TOC) (5–10 days after end of treatment) in the modified ITT population. The ITT population included all randomized patients and the modified ITT population included randomized patients who received any amount of study drug.

Overall, a total of 517 elderly patients aged ≥65 years were included in this analysis. Two hundred and sixty-eight and two hundred forty-nine elderly patients with CABP were randomized to receive lefamulin and moxifloxacin, respectively. The early clinical response rate was 91.0% (244/268) and 86.7% (216/249) among lefamulin and moxifloxacin group, respectively. No significant difference was observed between lefamulin and moxifloxacin [odds ratio (OR), 1.58; 95% confidence interval (CI), 0.90–2.75,  $I^2=0\%$ ] (*Figure 1*). The clinical response rate at TOC was 88.8% (237/267) and 83.5% (207/248) among lefamulin and moxifloxacin (OR, 1.61; 95% CI, 0.97–2.67,  $I^2=0\%$ ) (*Figure 1*).

In the subgroup analysis, no significant differences in terms of early clinical response rate was found between lefamulin and moxifloxacin for patients aged 65–74 years (OR, 2.12; 95% CI, 0.94–4.78,  $I^2=0$ ) and aged ≥75 years



**Figure 1** The early clinical response rate and clinical response rate among lefamulin and moxifloxacin group.

(OR, 1.18; 95% CI, 0.53–2.61,  $I^2=0$ ). Regarding the clinical responses rate at TOC, the similar trend was observed both subgroups (65–74 years, OR, 1.66; 95% CI, 0.77–3.56,  $I^2=24\%$ ;  $\geq 75$  years, OR, 1.53; 95% CI, 0.69–3.38,  $I^2=0\%$ ).

Based on this integrated analysis of LEAP 1 and LEAP 2 trials, we demonstrated that the clinical efficacy of lefamulin in the treatment of elderly patients with CABP was similar to moxifloxacin. The similarity of lefamulin to moxifloxacin was demonstrated in overall elderly population in different timing of outcome measurement—early clinical response at  $96\pm 24$  hours after first study drug dose and clinical response at TOC and also across the different age populations—aged 65–74 years and aged  $\geq 75$  years. In addition, the outcomes of elderly patients with CABP undergoing lefamulin treatment achieved to the clinical response rate of more than 88%. All of these findings indicated that lefamulin exhibited good efficacy in the treatment of elderly patients with CABP and should suggest that lefamulin can be considered as one of therapeutic options in this clinical condition.

This study has several limitations. First, only two studies with limited number of elderly patients were included in this study. Second, we did not assess the risk of adverse event, especially for gastrointestinal-related adverse event, which was more common in oral lefamulin group than moxifloxacin group. Further study is needed to investigate these issues. Third, subgroup analyses have well documented issues notable insufficient power and potential imbalances in prognostic factors. Therefore, we cannot

conclude noninferior from our data based on the lack of a prespecified margin and the issues with subgroup analyses.

In conclusion, the rates of clinical response were similar between the lefamulin and moxifloxacin treatment groups in patients  $\geq 65$  years of age. For elderly patients with CABP, this novel agent—lefamulin could be a therapeutic alternative in this clinical entity.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-19-3805>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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