Lefamulin Vs Moxifloxacin for Community-Acquired Bacterial Pneumonia

Background

- Community acquired bacterial pneumonia (CABP) is a leading cause of hospitalization and infection related mortality. It is usually treated with a respiratory fluroquinolone or a combination of B-lactams and a macrolide.
- Bacterial resistance with respiratory fluroquinolone is increasing for CABP
- Lefamulin is a novel pleuromutilin with in vitro activity against CABP pathogens but there are limited date regarding its clinical use for CABP.

Objective

- Two studies, Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2, were combined to better assess the clinical efficacy and safety of lefamulin for the treatment of CABP

Methods

- Design: Data were combined from two phase III double blind, double dummy, randomized, multicenter, multinational studies, LEAP 1 and LEAP 2 to increase the sample size. LEAP 1 used IV lefamulin 150 mg every 12 hours for 3 days followed by oral lefamulin 600 mg every 12 hours for 5-10 days total. This was compared with moxifloxacin 400 mg IV every 24 hours for 3 days followed by oral moxifloxacin 400 mg every 24 hours. LEAP 2 compared oral lefamulin at 600 mg every 12 hours for 5 days with oral moxifloxacin 400 mg every 24 hours for 7 days.
- Inclusion criteria:
    - LEAP 1: PORT class III and IV
    - LEAP 2: PORT classes II - IV
- Exclusion criteria:
    - Not mentioned in article
- Primary outcome measure: Early Clinical Response (ECR) proportion which was defined as survival with improvement in at least 2 signs and symptoms of CBP relative to baseline, no worsening of CABP, and no use of concomitant antibiotics other than the adjunctive linezolid. ECR was measured 96 ± 24 hours after the first dose of medication was given.
- Secondary outcome measure: Investigator's Assessment of Clinical Response (IACR) IACR was defined as resolution or improvement of a subject's clinical signs and symptoms such that no additional antibacterial therapy was administered for the treatment of the current episode of CABP
- Lefamulin and moxifloxacin groups were split up in the individual studies in 1:1 ratio, however, the study did not show
    - LEAP 1: > 90% power with 550 patients using a 1-sided alpha level of 0.025
    - LEAP 2: 91% power with 738 patients and had a 1-sided alpha level of 0.025
- Data handling: intent to treat for efficacy outcomes and a modified intent to treat (MITT) for safety outcomes if participants received 1 or more doses of study drug

Results:

- Primary outcome measure: 89.3 % and 90.5%for the ECR proportion for the lefamulin and moxifloxacin groups, respectively Lefamulin was noninferior to moxifloxacin (RR: 0.99, 95% CI: 0.95 – 1.02, I2=0%; Fig. 2). Noninferiority of lefamulin to moxifloxacin was concluded if the lower limit of the 95% CI for the treatment difference was >10%.

- Secondary outcome measure: No significant difference in clinical response in the MITT and the clinical evaluable (CE) populations (RR: 0.98, 95% CI: 0.94–1.02, I 2=0% , an RR: 0.96, 95% CI: 0.93–1.00, I 2=0% respectively) This CI refers to the clinical response in the MITT and CE populations.
- Risk of adverse effects: treatment-emergent adverse event (TEAE), RR: 1.14, 95% CI: 0.89 – 1.47, $I^2 = 61\%$.
- Serious adverse effects: RR: 1.16, 95% CI: 0.77-2.72, $I^2 = 79\%$
- Treatment related serious Adverse Effects: RR: 1.45, 95% CI: 0.17 – 0.74, $I^2 = 17\%$
- Treatment discontinuation due to TEAE: RR: 0.95, 95% CI: 0.45 – 1.88, $I^2 = 19\%$
- Treatment withdraw due to TEAE: RR: 0.63, 95% CI: 0.29 – 1.40, $I^2 = 0\%$
- Treatment leading to death: RR: 1.37, 95% CI: 0.55 – 3.39, $I^2 = 0\%$
- TEAE in moderate severity: RR: 1.41, 95% CI: 1.02 – 1.96, $I^2 = 79\%$
- Risk of nausea: RR: 2.03, 95% CI: 1.02-4.03, $I^2 = 6\%$
- Risk of diarrhea: RR: 1.06, 95% CI: .01 – 116.69, $I^2 = 96\%$

The results from the treatment related serious adverse effects and the TEAE in moderate severity were statically significant

Authors' conclusion: The clinical efficacy and tolerability for lefamulin for the treatment for CABP were non-inferior to moxifloxacin.

Strengths:

- Parallel study design
- Double blinded and double dummy
- Intent to treat which included all patients regardless of crossover or protocol violation

Limitations:

- Didn't list specific inclusion and exclusion criteria of each LEAP trial in this study
- Didn't assess cost effectiveness of Lefamulin
- Authors of this study did not have any conflicts of interest, however the authors from the original LEAP study, L. G., C. S., S. P. G., J. S., E. S., S. P., W. W. W., and L. B. G. were employees of Nabriva Therapeutics, the manufacturer of lefamulin, . A. D. and G. H. T. served as consultants for Nabriva Therapeutics during the design and execution of the study. G. H. T. is currently a member of the Board of Directors of Nabriva Therapeutics. Nabriva Therapeutics were involved in the analysis of the data from the LEAP trials.
- The durations of therapy in LEAP 1 and LEAP 2 were different.
- LEAP 1 used IV and oral lefamulin while LEAP 2 used only IV ORAL?? lefamulin. THIS MAKES IT MORE DIFFICULT to combine study results.

Conclusion:

To conclude, lefamulin was found be noninferior to moxifloxacin, however, the two studies did not use identical drug regimens for lefamulin and moxifloxacin. .It is unclear if it is beneficial to use lefamulin over moxifloxacin for CABP as the cost is seven times the cost of moxifloxacin

Reference:

Tang HJ, Wang JH, Lai CC. Lefamulin vs moxifloxacin for community-acquired bacterial pneumonia. *Medicine (Baltimore)*. 2020;99(29):e21223. doi:10.1097/MD.0000000000021223

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