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Lefamulin (Xenleta®) for community-acquired bacterial pneumonia (CABP)

by Stephanie Londre, PharmD

According to the World Health Organization, lower respiratory disease is the fourth leading cause of death worldwide.[1] At the same time, antibiotic resistance has emerged in several common pathogens that cause community-acquired bacterial pneumonia (CABP).[2] The general treatment modalities used for CABP, according to the 2019 CABP Infectious Diseases Society of American (IDSA) guideline, are beta-lactams, doxycycline, macrolides, or fluoroquinolones, depending on CABP severity and setting (outpatient versus inpatient).[3]

Lefamulin belongs to a class of antibiotics called pleuromutilins, which were first developed in the 1950s and have been used in veterinary medicine for more than 30 years.[4] The mechanism of action of lefamulin is unique, in that it binds to the 50S ribosomal subunit of bacteria to prevent peptide transfer. In 2019, the Food and Drug Administration (FDA) granted lefamulin approval for the treatment of CABP. Lefamulin is active against common CABP pathogens, including Streptococcus pneumoniae, Haemophilus influenza, Moraxella catarrhalis, Chlamydophila pneumoniae, Mycoplasma pneumonia, and Legionella pneumophila. Lefamulin also has activity against several antibiotic-resistant bacteria, including methicillin-resistant S. aureus (MRSA), vancomycin-resistant Enterococcus faecium (VRE), and multi-drug-resistant S. pneumoniae. Lefamulin is generally well-tolerated and is available in intravenous (IV) and oral formulations. Infusion site reactions (for the IV formulation), nausea, diarrhea, and increased liver function tests are noted to be the most common side effects of lefamulin.[5] There are several warnings and precautions associated with lefamulin use, including QT prolongation, embryo-fetal toxicity, and Clostridium difficile-associated diarrhea. However, the incidence of QT prolongation and Clostridium difficile-associated diarrhea in patients taking lefamulin is <2%.

CLINICAL QUESTION

Is lefamulin an effective treatment option for community-acquired bacterial pneumonia compared to standard of care?

Literature Review

Literature searches were executed in PubMed using the following search terms: "lefamulin" and "community-acquired bacterial pneumonia." The Lefamulin Evaluation Against Pneumonia (LEAP) 1 trial was a phase 3, double-blind randomized controlled trial (RCT) that evaluated the efficacy of lefamulin versus moxifloxacin for CABP.[6] The RCT included adult patients who had radiographically documented pneumonia, were categorized with a Pneumonia Outcomes Research Team (PORT) Risk Class ≥III, were ill for ≤7 days, had ≥2 vital sign abnormalities, and at least 1 other finding of CABP, and who initially needed IV antibiotics for CABP. For reference, PORT is a clinical prediction tool for morbidity and mortality for CABP. A total of 551 patients were randomized to receive lefamulin 150 mg IV every 12 hours (n=276) or moxifloxacin 400 mg IV every 24 hours (n= 275). After 3 days of IV treatment, patients were converted to oral lefamulin 600 mg every 12 hours, or moxifloxacin 400 mg every 24 hours, once predetermined benchmarks were met. Additionally, if MRSA was suspected, linezolid 600 mg IV every 12 hours was added to the moxifloxacin group.

The LEAP 2 trial was a phase 3, double-blind RCT that compared CABP treatment with lefamulin for 5 days to treatment with moxifloxacin for 7 days.[7] A total of 738 patients were randomized to receive lefamulin 600 mg by mouth every 12 hours for 5 days (n= 370) or moxifloxacin 400 mg by mouth every 24 hours for 7 days (n= 368). The RCT included adult patients who had radiographically documented pneumonia, were categorized with a PORT Risk Class ≥II, were ill ≤7 days, had ≥3 CABP symptoms, and had ≥2 vital sign abnormalities.

In both LEAP 1 and LEAP 2, the FDA primary endpoint was early clinical response (ECR).[2] ECR was defined as an improvement in ≥2 CABP symptoms without any worsening CABP symptoms, and no other antimicrobial use 96 ±24 hours after the first dose of the study treatment. Additionally, the European Medicines Agency (EMA) co-primary endpoints were the investigator assessment of clinical response (IACR) at the test of cure in both the modified intention to treat population (mITT) and the clinically evaluable (CE) populations. IACR was defined as an improvement of CABP without the use of other antimicrobials 5-10 days after the last dose of the study treatment. The mITT population was defined as all randomized patients who received at least one dose of the study drug, and the CE population consisted of patients who met the following criteria: no indeterminate clinical response, completion of at least 48 hours of treatment with the

study drug, and no additional antibiotics received.

In a pooled analysis of both LEAP 1 and LEAP 2, lefamulin was found to be non-inferior for ECR (89.3% vs 90.5%; difference -1.1, 95% confidence interval [CI] -4.4 to 2.2) compared to moxifloxacin.[2] In LEAP 1, the non-inferiority margin for ECR was 12.5%.[6] Compared to moxifloxacin, lefamulin was found to be non-inferior for ECR (87.3% vs 90.2%, respectively; difference -1.9%, 95% confidence interval [CI] -8.5 to 2.8). In both the mITT and CE populations, the non-inferiority margin for IACR at the test of cure was 10%. Lefamulin was found to be non-inferior to moxifloxacin for IACR at the test of cure in the mITT population (81.7% vs 84.2%, respectively; difference -2.6%, 95% CI -8.9 to 3.9) and the CE population (86.9% vs 89.4%, respectively; difference -2.5%, 95% CI -8.4 to 3.4). In LEAP 2, the non-inferiority margin was 10% for both ECR and IACR. Lefamulin was found to be non-inferior to moxifloxacin for ECR (90.8% vs 90.8%, respectively; difference, 0.1%, 1-sided 97.5% CI -4.4% to ∞) and IACR (mITT 87.5% vs 89.1%, respectively; difference -1.6%, 1-sided 97.5% CI -6.3 to ∞; CE 89.7% vs 93.6%, respectively; difference -3.8%, 1-sided 97.5% CI -8.2% to ∞).[7]

A limitation of the LEAP 1 trial was the addition of linezolid IV when MRSA was suspected, because most institutions prefer vancomycin over linezolid for MRSA coverage. Thus, the actual population of patients with CABP and MRSA risk factors may not be accurately represented. The authors of this study concluded that lefamulin monotherapy was as efficacious for CABP as moxifloxacin ± linezolid. Lefamulin showed high response rates for common CABP pathogens and was well tolerated. A limitation of the LEAP 2 trial was its baseline characteristics, because most patients enrolled were white (74.1% in the lefamulin group and 73.4% in the moxifloxacin group). The authors of this study concluded that lefamulin is an effective alternative CABP therapy option.

Evidence-based answer: Lefamulin is non-inferior to moxifloxacin for CABP (Strength of recommendation = A, based on consistent high-quality, patient-oriented evidence from RCTs). Current literature is lacking, however, as moxifloxacin is not the standard of care for outpatients with CABP who do not have comorbidities, according to the 2019 CABP IDSA guideline. Thus, further research comparing lefamulin to amoxicillin, doxycycline, or macrolides is needed to fully answer the clinical inquiry question.

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