Lefamulin, a recently approved novel antibacterial agent to fight against community-acquired bacterial pneumonia

Sir,

Community-acquired bacterial pneumonia (CABP), a potentially serious respiratory infection, is a leading cause of hospitalization worldwide, and despite antibiotic treatment, it is still a relevant cause of death.[1] *Streptococcus pneumoniae* is the most commonly isolated pathogen associated with CABP; other common pathogens include *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* along with atypical pathogens like *Chlamydophila pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumonia*. Currently, India accounts for 23% of the global pneumonia burden and 36% of the World Health Organization regional burden. Reported incidence rate of CABP in India is nearly 4 million cases/year.[2]

Current recommendations for the treatment of CABP mainly focus on initiation of empirical antibiotic therapies. The American Thoracic Society and Infectious Diseases Society of America clinical guideline on the diagnosis and treatment of adults with community-acquired pneumonia recommend usage of beta-lactam, macrolide, and fluoroquinolones more commonly according to severity, comorbidities.[3] However, newer class of drug is need of the hour due to the continued presence of resistance, re-emergence of previous pathogens in addition to new ones, high rate of treatment failure, and adverse reactions of the existing molecules.

In this regard, Lefamulin is a novel first-in-class, systemic, semi-synthetic pleuromutilin antibiotic designed to inhibit the synthesis of bacterial protein. It was approved by the Food and Drug Administration (FDA) on August 19, 2019, to treat adult patients with CABP. The drug is designed to be given either intravenously (150 mg twice daily for 5–7 days) or orally (600 mg twice daily for 5 days). It has high oral bioavailability with a biologic half-life of 12 h and is largely excreted via the gastrointestinal tract (86%) in its unchanged form.[4]

Lefamulin inhibits translation by binding to the A- and P-site of the peptidyl transferase center of the 50S subunit of the bacterial ribosome via four H-bonds and other interactions resulting in an "induced fit." It selectively inhibits bacterial ribosomal translation but does not affect eukaryotic ribosomal translation. This unique mechanism of action has been associated with a low probability of cross-resistance to other antimicrobials.[5] The antibacterial spectrum of lefamulin covers both typical Gram-positive and fastidious Gram-negative respiratory pathogens and atypical pathogens. The SENTRY Antimicrobial Surveillance Program demonstrated potent antimicrobial activity for lefamulin against acute bacterial skin and skin structure infection and CABP.[1]

Of late, two multicenter, randomized, double-blind, double-dummy, Phase 3 trials – lefamulin evaluation against pneumonia (LEAP 1 and LEAP 2) – evaluated lefamulin as monotherapy for the treatment of adult patients with CABP. LEAP 1 evaluated the safety and efficacy of intravenous lefamulin (150 mg) twice daily versus intravenous moxifloxacin (400 mg) once daily (with or without linezolid) in 551 adults with moderate-to-severe CABP (Pneumonia Patient Outcomes Research Team [PORT] Risk Class III), with the option of switching to oral administration. Lefamulin was non-inferior to moxifloxacin for early clinical response ([ECR] 87.3% vs. 90.2%, respectively; difference −2.9%, 95% confidence interval [CI] −8.5–2.8) and investigator assessment of clinical response ([IACR] modified intention to treat [mITT], 81.7% vs. 84.2%, respectively; difference −2.6%, 95% CI −8.9–3.9; clinically evaluable (CE), 86.9% vs. 89.4%, respectively; difference −2.5%, 95% CI −8.4–3.4).[6]

LEAP 2 compared the safety and efficacy of 600 mg of oral lefamulin twice daily for 5 days versus 400 mg of oral moxifloxacin once daily for 7 days in 738 adult patients with moderate CABP (PORT Risk Class II–IV). The FDA primary endpoint was ECR at 96 h after the first dose, whereas the secondary endpoints were IACR at the test of cure. ECR rates were 90.8% with lefamulin and 90.8% with moxifloxacin (difference, 0.1% [one-sided 97.5% CI: −4.4% to ∞]). Rates of IACR success were 87.5% with lefamulin and 89.1% with moxifloxacin in the mITT population (difference, −1.6% [one-sided 97.5% CI: −6.3% to ∞]) and 89.7% and 93.6%, respectively, in the clinically evaluable population (difference, −3.9% [one-sided 97.5% CI: −8.2% to ∞]) at the test of cure. Both the clinical trials met efficacy endpoints for noninferiority and provided evidence that lefamulin was generally well tolerated [Table 1]. Few commonly encountered adverse effects were mainly diarrhea, nausea, and elevation liver enzymes.[7] In conclusion, this drug promises to be a new hope in treating CABP in future due to its unique features such as new class of molecule with novel mechanism, complete spectrum of coverage, well-tolerated profile, excellent pharmacological parameters with mild food interaction, no loading dose, no dose adjustment, and convenience of use in both hospital or community settings due to the availability of parental and oral preparations and short course of monotherapy. Although high cost would prohibit large-scale usage, expanded data on safety/efficacy is still required.

Table 1: Efficacy results (% responders) in LEAP 1 & 2 comparing FDA vs EMA primary end-points

Study[a]	Comparators[b]	FDA primary end-point	EMA c0-primary end-point (s)	
		ECR in ITT	IACR at TOC (mITT)	IACR at TOC (CE)
LEAP 1	Lefamulin	87.3	81.7	86.9
	Moxifloxacin (± Linezolid)	90.2	84.2	89.4
		Delta (95% CI) = -2.9 (-8.5, 2.8)	Delta (95% CI) = -2.6 (-8.9, 3.9)	Delta (95% CI) = -2.5 (-8.4, 3.4)
LEAP 2	Lefamulin	90.8	87.5	89.7
	Moxifloxacin	90.8	89.1	93.6
		Delta (95% CI) = 0.1 (-4.4, 4.5)	Delta (95% CI) = -1.6 (-6.3, 3.1)	Delta (95% CI) = -3.9 (-8.2, 0.5)

Numerical data expressed as %. LEAP, Lefamulin Evaluation Against Pneumonia; FDA, Food & Drug Administration; EMA, European Medicines Agency; ECR, Early Clinical Response; IACR, Investigator Assessment of Clinical Response, ITT, Intention to Treat; mITT, Modified Intention to Treat; CE, Clinically evaluable; TOC, Test of Cure. [a]Lefamulin met all primary end-points (FDA & EMA) in LEAP 1& 2; [b]High response rate seen in both arms

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Conflicts of interest
There are no conflicts of interest.

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