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Short Commucation

A Systematic Review on Nafithromycin: A Novel Lactone Ketolide Antibiotic for Drug Resistant Pneumonia

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A B S T R A C T

Background: Community-acquired bacterial pneumonia is one of the leading causes of mortality and morbidity in the elderly. Widespread macrolide resistance mechanisms in Streptococcus pneumoniae have challenged their empirical utility. Nafithromycin, India's first indigenously developed lactone-ketolide by Wockhardt, received approval from the Central Drugs Standard Control Organization on January 1st, 2025, for community-acquired bacterial pneumonia caused by drug-resistant bacteria. Nafithromycin, with a unique structure, inhibits bacterial protein synthesis by targeting the 50S subunit of the 70S ribosome.

Aim: To review the available literature on clinical, microbiological and pharmacokinetic evidence of nafrithromycin in the treatment of community-acquired bacterial pneumonia.

Objective: 1. To review the clinical efficacy. 2. To review the safety and tolerability of nafithromycin.

Methodology: A comprehensive literature search was conducted using PubMed, Google Scholar and clinical trial registries for studies published during 2019-2024. Both preclinical studies and clinical trials were included. Data extracted on antimicrobial activity, pharmacokinetics, safety, resistance mechanisms and efficacy.

Results: 13 relevant studies were identified, including a phase-3 clinical trial, which showed nafithromycin's unique structure and pharmacokinetics supporting once-daily dosing, short duration and better patient compliance with minimal side effects.

Conclusion: This systematic review highlights the potent activity of naftithromycin against resistant pathogens, favourable safety and short-course therapy in treating CABP.

Keywords: Nafithromycin, WCK 4873, Macrolide Resistance and Community-Acquired Bacterial Pneumonia (CABP)

Introduction

Community-acquired bacterial pneumonia is one of the leading causes of mortality and morbidity with significant impact on the health care system. India is accounting for approximately 23% of the global community-acquired pneumonia burden, with an annual incidence of around 4 million new cases.[1,2,3] Streptococcus pneumoniae being the most common cause, other typical bacteria like Haemophilus influenzae and Moraxella catarrhalis and atypical bacteria like Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella pneumophila are also significant. Macrolides have been a mainstay of treatment for community-acquired pneumonia. However, their clinical use has become limited due to the emergence of antibiotic resistance. [4] Nafithromycin, India's first indigenous lactone-ketolide antibiotic, with a unique naphthyl group inhibiting bacterial protein synthesis, has shown potent antimicrobial activity against multidrug-resistant pneumococcal strains by overcoming the macrolide resistance mechanisms, namely Erm, efflux and ribosomal protein mutations in Streptococcus pneumoniae. [5,6] It has also shown consistent activity against β-lactam and quinolone-resistant Streptococcus pneumoniae, Haemophilus influenzae and atypical respiratory pathogens[6] . Nafithromycin was approved by CDSCO on January 1st, 2025, for community-acquired bacterial pneumonia, acute bacterial exacerbations of chronic bronchitis and acute bacterial sinusitis and pharyngitis in adults more than 18 years old.

Aim

To review the available literature on clinical, microbiological and pharmacokinetic evidence of nafrithromycin in the treatment of community-acquired bacterial pneumonia.

Objective

- To review the clinical efficacy of nafithromycin in community-acquired bacterial pneumonia.
- To review the safety and tolerability of nafithromycin across preclinical and clinical studies.

Methodology

A comprehensive literature search was done through PubMed, Google Scholar and clinical trial registry using 'nafithromycin', 'WCK 4873', 'macrolide' resistance and community-acquired bacterial pneumonia (CABP)' as keywords. Included preclinical studies, peer-reviewed original research articles, pharmacokinetic analyses and clinical trials. Data on clinical efficacy, safety, pharmacokinetic, and resistance mechanisms were extracted. Excluded case reports and conference abstracts, studies lacking relevant data and duplicate publications.

Results

Nafithromycin's unique structure, lacking L-cladinose and featuring a rigid spacer with a biaryl side chain, enhanced its binding to dual sites at bacterial ribosomal domain V, like conventional macrolides and at domain II with a novel amidoxime function-bearing 2-pyridine-1,3,4-thiadiazole biaryl side chain in 23 rRNA of the 50S subunit of the 70S ribosome, enabling strong activity against resistant Streptococcus pneumoniae, including erm-B-expressing and telithromycin-resistant strains.[7]

In preclinical studies, nafithromycin was well-tolerated and has shown a better hepatic safety profile as observed in 4-week repeat-dose toxicity studies in Wistar rats and beagle dogs. As a non-inducer of major cytochrome P450 enzymes, nafitromycin reduces the hepatotoxicity by minimising the drug interactions that liberate hepatotoxic metabolites with these enzymes. [8]

In a phase-1 pharmacokinetic study, nafithromycin showed high pulmonary exposures observed during and within 48 hrs after once-daily, three-day dosing, providing a rationale to consider it for a short treatment course in the treatment of CABP. [9]

In a double-blind randomised controlled phase-1 clinical trial, nafithromycin exhibited MIC_{50} values of 0.015–0.03 mg/L and MIC_{90} of 0.06 mg/L against Streptococcus pneumoniae including strains with erm(B) and mef (A/E)-mediated resistance and a half-life of 9.16 to 14.4 hours with excretion primarily through faeces and to some extent through urine. Adverse events were mild and self-limiting, like diarrhoea, nausea and headache. [10]

Nafithromycin also exhibited anti-inflammatory properties in lung tissue in murine models, suggesting its added benefit in severe infection.[11]

In an in vitro study in India on 534 isolates with 59 erythromycin-non-susceptible isolates having erm(B) and mef(A/E) genes in 49% and 59% of strains, respectively and few penicillin and quinolone-resistant strains, azithromycin and clindamycin showed limited activity, whereas nafrithromycin showed potent activity with MIC_{50} and MIC_{90} of 0.015–0.03 and 0.06 mg/L, regardless of the macrolide resistance mechanisms.[12]

In another in vitro study, with a large collection of Streptococcus pneumoniae isolates originating from three different centres in China containing >80% of isolates resistant to both macrolides and clindamycin, nafithromycin showed potent activity with all isolates.[13]

In a phase-III multicentric randomised clinical trial with CTRI registration number CTRI/2019/11/021964, an 800 mg tablet of nafithromycin was given once a day for three

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days to subjects ≥18 years old with community-acquired bacterial pneumonia, shown to be as non-inferior to 7 days of 400 mg once daily moxifloxacin.[14]

Discussion

Macrolide resistance has compromised monotherapy for CABP, often requiring less effective combinations with β-lactams. Nafithromycin was shown as a convenient 3-day monotherapy in recent studies supporting this review to assess available literature on the drug. Nafithromycin's potential to reduce hospitalisation and healthcare burden can overcome a critical gap in the management of CABP in the era of rising antimicrobial resistance. Its potent in vitro activity and favourable pharmacokinetic profile support its role as a first-line agent in CABP. A shorter treatment plan enhances patient adherence and lessens the burden on healthcare systems. In comparison to macrolides and fluoroquinolones, nafithromycin seems to achieve higher concentrations in lung tissue, has a reduced likelihood of causing hepatotoxicity and QT prolongation and is a weaker inhibitor of Cytochrome P3A4 relative to other ketolide antibiotics such as telithromycin and solithromycin, thus helping to minimise drug interactions.

Strengths and limitations:

A concise review on a novel, clinically approved antibiotic based on the latest (2025) regulatory data. Comprehensive inclusion of pharmacokinetic, microbiological and clinical efficacy studies. Relevance to India and other regions facing high macrolide resistance. However, further large-scale, multi-centric clinical trials and post-marketing surveillance for long-term follow-up are needed.

Conclusion

Nafithromycin, a major advancement in pneumonia treatment in 30 years and a significant milestone in the global fight against antimicrobial resistance, is potent, safe and convenient for community-acquired bacterial pneumonia against resistant pathogens.

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