Original Article

Lefamulin – upgrading our arsenal against community-acquired pneumonia

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Abstract

Lefamulin (formerly BC-3781) is a novel semi-synthetic pleuromutilin antibiotic that has been granted marketing authorization in the US for the treatment of patients with Community-acquired bacterial pneumonia (CABP). It shows potent *in vitro* activity against atypical and typical pathogens that cause CABP. Lefamulin interferes with the peptidyl transferase center and inhibits the prokaryotic ribosomal protein synthesis. This is achieved through its binding at the A- and P-site of the 50S ribosomal submit, resulting in the interruption of peptide bond formation. This is a novel mechanism for inhibiting bacterial peptide chain elongation. By virtue of its favorable clinical response and reasonable safety data in two non-inferiority phase III clinical trials (Lefamulin Evaluation against Pneumonia - LEAP1 & LEAP2 trials), the drug has been granted regulatory approval. The drug is highly bound to plasma protein and the mean half-life is 8 hours. The drug is metabolized by cytochrome P450 (CYP450) enzyme. This narrative review discusses the efficacy, safety, pharmacokinetics, and current status of lefamulin in the management of CABP.

Keywords: Lefamulin, LEAP1, LEAP2, community-acquired bacterial pneumonia

Introduction

Pneumonia is a disease infecting the lung parenchyma and is one of the main causes of morbidity, hospital admissions and readmissions, and mortality. [1-3]. Community-acquired bacterial pneumonia (CABP) could unleash a myriad of complications that could be fatal or cause profound morbidity [4]. The double whammy of pneumonia and influenza is the 9th major cause of death overall and the most common cause of infectious death in the USA, causing an estimated 50000 deaths in 2010 [5]. *Streptococcus pneumoniae*, *Moraxella catarrhalis,* and *Haemophilus influenzae* are the three major bacterial pathogens causing CABP [6-9]. These bacterial pathogens effectively resist a number of existing antibiotics available in the market.

Streptococcus pneumonia is reported to be the most prevalent cause of pneumonia when compared to the other two pathogens [10, 11]. *S. pneumoniae* has shown resistance towards various antibiotics such as β-lactams, clindamycin, tetracyclines, and macrolides, with resistance rates up to 40% [12]. *H. influenzae* has shown resistance towards various antibiotics such as trimethoprim-sulfamethoxazole, clarithromycin, azithromycin, tetracycline, cefaclor, chloramphenicol, co-trimoxazole, ampicillin, tetracycline, amoxicillin, cefixime, and ciprofloxacin [13-15]. *M. catarrhalis* has shown resistance towards various antibiotics including quinolones, macrolides, chloramphenicol, tetracycline, TMP-SMX, and rifampin [16-18]. The World Health Organization (WHO) estimates that antimicrobial resistance on account of bacterial infections will have the dubious distinction of being the leading cause of death by 2050 [19, 20]. Hence, identifying new strategies to develop antibiotics should be done with much alacrity than before.

It is heartening to note that the US Food and Drug Administration (FDA) has permitted the marketing of a novel antibiotic named lefamulin to treat adults with community-acquired bacterial pneumonia in August 2019 [21]. Lefamulin belongs to a group of molecules, which are termed as pleuromutilins, which were isolated from the basidiomycete fungi *Clitopilusscyphoides* and *Clitopilus passeckerianu* [22]. Practitioners of veterinary medicine have been extensively utilizing pleuromutilins for more than three decades. Resistance to these drugs has been uncommon [23].

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Pleuromutilins are also produced from organisms such as *Psathyrella conopilus* and other *Clitopilus* species. The earliest semi-synthetic pleuromutilins developed were tiamulin and valnemulin. They continue to be used to date [22].

Chemistry ($C_{28}H_{45}NO_5S$)

Studies have shown that the element of the C-14 side chain largely plays the characteristic role of antimicrobial action and pharmacokinetics (PK) such as permeability, oral bioavailability, plasma protein binding, and metabolism. Lefamulin was first synthesized as 14-O-[(1R,2R,4R)-4-amino-2-hydroxycyclohexylsulfanyl]-acetyl-mutilin in 2006 [21] [Fig. 1]. The C-14 side chain of lefamulin appears to be instrumental in its ability to attain systemic efficacy. The number of pleuromutilin derivatives has been studied to map out the structure and activity relationships with particular importance noted at the carbon-14 side chain in past decades [24]. The pleuromutilin antibiotic compound has a fused 5-6-8 tricyclic diterpenoid structure [25] [Table 1].

Mode of Action

Lefamulin, an antibiotic formulated by Nabriva Therapeutics, is a semi-synthetic derivative of pleuromutilin [22]. It is mainly used to treat CABP and acute bacterial skin and skin structure infections [21]. The chemical structure consists of tricyclic mutilin core moiety, essential for antimicrobial activity mainly because of complex interaction with the central part of the 23S subunit of ribosomal RNA through hydrophobic interactions, hydrogen bonding, and the van der Waal forces [24, 26]. The Carbon-14 (C-14) side chain is the principal factor for the pharmacodynamic and antimicrobial properties of this drug. Lefamulin can be administered either by intravenous infusion or oral routes due to the side chain comprises of thioether bond, allowing to influence antimicrobial activity, intensify solubility, and optimized metabolic stability [27]. The C-14 side chain plays a key role in reducing antibiotic resistance by enhancing the number of hydrogen bonds to the target site and bacterial ribosomal mutations.

Lefamulin interferes with the peptidyl transferase center and binds to the A- and P-site of the 50S ribosomal submit. As a consequence, the formation of the peptide bond is hindered. This is a novel mechanism to inhibit the elongation of the bacterial peptide chain, principally the formation of the first peptide bond. It does not, however, have any effects on the elongation peptide chain after it has begun [26]. Lefamulin has shown bacteriostatic properties against most organisms, gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* [28], as well as *Moraxella catarrhalis*, *Haemophilus influenzae* and atypical pathogens including *Legionella pneumophila, Mycoplasma pneumonia,* and *Chlamydophila pneumonia* [29].

Efficacy:

Lefamulin has been evaluated for its efficacy in two Phase 3 clinical trials namely the LEAP 1 and LEAP 2 trials, both of these trials used a non-inferiority study design [30]. The LEAP 1 trial compared lefamulin with moxifloxacin. In this trial, initially both the drugs were given as IV infusion and later switched over to oral route after 6 doses. 551 patients were randomized to either moxifloxacin or lefamulin in a 1:1 ratio [31]. Lefamulin was found to be non-inferior to moxifloxacin as measured by early clinical response rate (87.3 % vs 90.2%, a difference of -2.9 % and a confidence interval of -8.5 to 2.8. The non-inferiority margin that was fixed for this endpoint was 12.5%. Similarly, lefamulin showed non-inferiority to moxifloxacin in the EMA driven primary endpoint of investigator assessment of clinical response (IACR – 81.7% vs 84.2%; the difference of -2.6% and a confidence interval of -8.9 to 3.9. The non-inferiority margin that was fixed was 10% for this end point [31].

The LEAP 2 trial compared oral lefamulin with moxifloxacin using a similar non-inferiority design in 738 patients with CABP. Patients randomly received either moxifloxacin 400mg every 24h for 7days or lefamulin 600mg every 12h for 5days or. Early clinical response was comparable between the 2 groups (90.8 vs 90.8%). The IACR was also not much different between the two groups – lefamulin 87.5% vs. moxifloxacin 89.1%. The 5-day therapy had a response that was non-inferior to the 7-day moxifloxacin regimen [32].

LEAP trials did have a number of drawbacks. For instance, very few patients were included with an increased risk of mortality associated with high PORT risk class and CURB-65 score. It is not known if there were any deaths that occurred among study groups. The exclusion of high-risk participants would also have minimized deaths to a large extent. These studies primarily included patients from Eastern Europe and had poor representation from the rest of the world. The drug was offered to treat naïve subjects and even excluded patients with a recent history of hospital admission for CABP. This study excluded patients requiring mandatory mechanical ventilation or those with empyema or other major co-morbidities. Future investigations are needed to explore the value of lefamulin in these settings. On a positive note, lefamulin showed good antimicrobial activity against all the common pathogens such as *S. pneumoniae, S. aureus, H. influenzae, M. catarrhalis*, and even atypical organisms such as *M. pneumonia, C. pneumonia,* and *L. pneumophila*.

Safety

The injection reactions occurred in 7% and 3% of cases treated with IV lefamulin and IV moxifloxacin respectively. Diarrhea was prevalent with oral lefamulin (12% vs 1% with moxifloxacin). The rate of hepatic enzyme elevations, insomnia, hypokalemia, headache, and nausea did not differ much between the two groups in the LEAP trials especially if higher-than-recommended doses are used or if the drug is infused too fast. It is preferable to restrict the use of lefamulin in patients with ventricular arrhythmias or QT interval prolongation, including torsades de pointes, and in those taking Class IA or III antiarrhythmic drugs or other medicines, which prolong the QT interval. In individuals with risk factors for QT interval prolongation, if the use of

lefamulin cannot be avoided, ECG monitoring is recommended during treatment [33].

Pharmacokinetics

Lefamulin achieves excellent penetration in the epithelial lining fluid (ELF) of the lungs and has high intracellular concentrations in macrophages. It also shows potent *in vivo* benefits in mouse models of pulmonary infection [34-36]. Lefamulin has a bioavailability of 25% and it takes 0.88-2hours to reach peak plasma concentration [37]. Food causes a considerable reduction in the bioavailability of lefamulin. The drug is highly bound to plasma protein and the mean half-life is 8 hours. The drug is metabolized by cytochrome P450 (CYP450) enzymes. Hence, strong inducers of CYP3A4 such as rifampicin can decrease the concentration of lefamulin and strong inhibitors of CYP3A4 can increase the concentration of lefamulin [38]. There is no effect of age, gender, race, and renal impairment on the pharmacokinetics of lefamulin. However, the half-life of the drug is prolonged in people with hepatic dysfunction. Thus, it is prudent to avoid using lefamulin in patients with severe hepatic dysfunction [39].

Current status

FDA approved lefamulin for both oral/IV on August 19, 2019. The drug is under review for approval by the European Medicines Agency [40]. A phase 2 trial on the efficacy of lefamulin for the treatment of Skin Structure Infections and Acute Bacterial Skin has been completed [41]. The results have not yet been published. Lefamulin has also been explored in other indications such as hospital-acquired bacterial pneumonia & ventilator-associated bacterial pneumonia, sexually-transmitted infections, osteomyelitis, and prosthetic joint infections [42].

Limitations

So far, no studies have been conducted on the use of lefamulin in pregnant women. In animal studies, administration of lefamulin during pregnancy led to stillbirth, fetal loss, and decreased fetal ossification and body weight. There was also a marked delay in sexual maturation in rats. According to the label, women who can become pregnant should take effective contraceptives while taking lefamulin and for 2days after stopping it. It has been reported that lefamulin is present in the milk of lactating rats. Since it has the potential to cause serious side effects in infants, including QT interval prolongation, mothers who breastfeed should be advised to pump and discard breast milk during and for 2days after taking the last dose of lefamulin treatment [43, 44].

Conclusion

Lefamulin is a novel pleuromutilin antibiotic that has favorable activity against a number of gram-positive, fastidious gram-negative microorganisms including respiratory bacterial pathogens associated with CABP. The approval of an antibiotic after a long hiatus of more than a decade is a welcome trend, considering the apparent lack of enthusiasm for big pharmaceutical companies to discover novel antibiotics. Older, less expensive antibiotics with a longer history of efficacy and safety are generally preferred for empiric treatment of CABP. Nevertheless, the antimicrobial activity, PK parameters, and reasonable safety make it a suitable alternative for patients with CABP.

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Table 1. Summary of the pharmacological characteristics of lefamulin

Pharmacology	
class	Pleuromutilin antibiotic
Trade name	Xenleta
Formula	$C_{28}H_{45}NO_5S$
Other name	BC - 3781
ATC	J01XX12 (WHO)
Route	IV and PO
formulation	150mg single- dose vials ; 600 mg tablets
Injection	Clear, colorless solution in a single-dose clear glass vial. Each vial contains 150mg lefamulin in 15mL of 0.9% sodium chloride for further dilution
Tablets	Blue, oval, film-coated tablet with 'LEF 600' printed in black on one side. Each tablet contains 600 mg of lefamulin.
bioavailability	Po : 0.88-2 hours
T_{max}	Po: 0.88-2 hours
Metabolism	Primarily by CYP3A4
Excretion	IV: Faeces (77%);urine (16%) & PO: Feces (89%); urine (5%)
Half-life	~8 hours

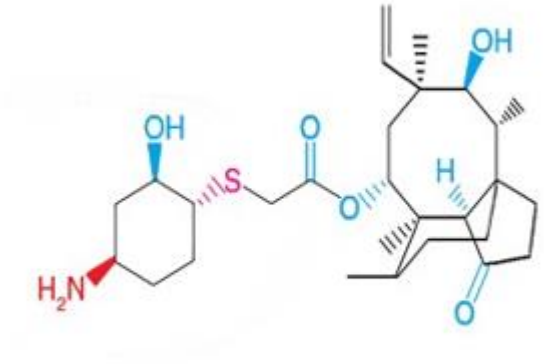

Figure 1: Chemical structure of lefamulin (BC-3781)