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Lefamulin vs moxifloxacin for community-acquired bacterial pneumonia

Hung-Jen Tang, MD[a], Jui-Hsiang Wang, MD[b], Chih-Cheng Lai, MD[b,*]

Abstract

Lefamulin is a novel pleuromutilin antibiotic with potent in vitro activity against key community-acquired bacterial pneumonia (CABP) pathogens. However, the clinical efficacy and safety of lefamulin for treating CABP remains unclear.

An integrated analysis of 2 phase III trials investigating the clinical efficacy and safety of lefamulin vs moxifloxacin in the treatment of CABP was conducted.

A total of 1289 patients (lefamulin group: 646 and moxifloxacin group: 643) were included in this analysis. The early clinical response rate was 89.3% and 90.5% among lefamulin and moxifloxacin group, respectively. Lefamulin was noninferior to moxifloxacin (89.3% vs 90.5%, RR: 0.99, 95% CI: 0.95–1.02, $I^2=0\%$). In terms of clinical response at test of cure, no significant difference was observed between the lefamulin and moxifloxacin groups (for modified intention to treat population, RR: 0.98, 95% CI: 0.94–1.02, $I^2=0\%$; for clinically evaluable population, RR: 0.96, 95% CI: 0.93–1.00, $I^2=0\%$). In the subgroup analysis, the early clinical response rate at early clinical assessment and clinical response rate at test of cure of lefamulin was similar to that of moxifloxacin across different subgpopulations and all baseline CABP pathogens. Lefamulin was associated with a similar risk of adverse events as moxifloxacin.

Clinical efficacy and tolerability for lefamulin in the treatment of CABP were similar to those for moxifloxacin.

Abbreviations: CABP = community-acquired bacterial pneumonia, PORT = pneumonia outcome research team, TOC = test of cure.

Keywords: community-acquired bacterial pneumonia, lefamulin, moxifloxacin

1. Introduction

Community-acquired bacterial pneumonia (CABP) remains a global health threaten, and is a leading cause of hospitalization and infection-related mortality.[1] This type of infection is commonly caused by the typical pathogens - *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and the atypical pathogens - *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*.[2] Empirical treatment regimen of CABP typically involves either a respiratory fluoroquinolone or a combination of β-lactams and a macrolide.[2–4] However, like other types of infections, antimicrobial resistance has reduced the effectiveness of commonly used antibiotic and become another serious concern in the treatment of CABP. The emergence of antibiotic-resistant organism – penicillin-resistant *S. pneumoniae*, methicillin-resistant *S. aureus*, macrolide-resistance in *M. pneumoniae*, and levofloxacin-nonsusceptible *S. pneumoniae* makes the condition more complicated than before.[5–7] All of these issues triggered the urgent need of a newly effective antibiotic for treating CAPB.

Lefamulin is a promising novel pleuromutilin antibiotic, which exhibits a unique mechanism of action through inhibition of protein synthesis and further preventing the binding of transfer RNA for peptide transfer.[8] Several in vitro studies[9–11] have demonstrate its potent activity against commonly encountered CAPB pathogens, even for antibiotic-resistant bacteria. However, the clinical study investigating the usefulness of lefamulin in the treatment of infectious disease is limited. Until now, only two randomized clinical trials[12,13] assess the uses of lefamulin in the treatment of CABP. Both of these two studies[12,13] used moxifloxacin as comparator. Moxifloxacin is an extended-spectrum fluoroquinolone which exhibit potent activity against gram-positive cocci and atypical pathogen and recommended as a respiratory fluoroquinolone in the treatment of CABP.[14–16] To better understand the clinical efficacy and safety of lefamulin, we conducted this integrated analysis of two phase III studies[12,13] investigating the usefulness of lefamulin in the treatment of CABP.

2. Methods

2.1. The characteristics of the studies

The Lefamulin Evaluation Against Pneumonia (LEAP) program comprised 2 phased III randomized, multicenter, multinational

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Ethical approval was not required.

Informed consent was not required.

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

[a] Department of Medicine, Chi Mei Medical Center, [b] Department of Internal Medicine, Kaohsiung Veterans General Hospital, Tainan Branch, Tainan, Taiwan.

[*] Correspondence: Chih-Cheng Lai, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Tainan Branch, Tainan, Taiwan (e-mail: dtmed141@gmail.com).

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studies – LEAP 1 (NCT02559310) and LEAP 2 (NCT02813694).[12,13] LEAP 1 included adult patients with CABP at pneumonia outcome research team (PORT) risk class ≥ III. This trial compared the clinical efficacy and tolerability of Lefamulin (150 mg intravenous [IV], every 12 hours) and moxifloxacin (400 mg IV every 24 hours). On or after 3 days (6 doses) of IV treatment, patients could be switched to oral lefamulin 600 mg q12 hours or moxifloxacin 400 mg q24 h and the total duration of antibiotic treatment ranged from 5 to 10 days.[13] LEAP 2 included adult patients with CABP at PORT risk class II, III or IV and compared the effect and safety of oral lefamulin (600 mg every 12 hours for 5 days) and oral moxifloxacin (400 mg every 24 hours for 7 days).[12] This study study was exempt from ethics approval of Chi Mei Medical center as the study authors just collected and synthesized data from previous clinical trials in which informed consent has already been obtained by the trial investigators.

2.2. Analysis population and outcome measurement

The intent-to-treat (ITT) population included all patients who were randomized and the modified intent-to-treat (MITT) population was the population to assess adverse events and comprised all patients who received 1 or more doses of study drug. The microbiologic (mITT) population included all patients in the ITT population had a baseline qualifying bacterial pathogen. The clinically evaluable (CE) population included patients who received study drug for a total duration of 48 hours or longer (unless patient died prior to 48 hours), and had assessable efficacy. Efficacy endpoints included: proportion of patients with early clinical response (ECR) at early clinical assessment and clinical response at the end of treatment (EOT) and test of cure (TOC) (5–10 days after EOT). ECR responders was defined as improvement in ≥2 of 4 CABP signs/symptoms, had no worsening in any CABP sign/symptom, and had not received other non-study antibiotic for CABP at 96 ± 24 hours after first study drug dose. Clinical responder was defined as successful if resolution or improvement of CABP signs/symptoms and no additional antibiotics was needed for CABP.

2.3. Statistical analysis

Categorical variables were reported as frequency counts with percentages. In addition, the differences of baseline characteristics between the lefamulin and moxifloxacin groups were evaluated using Pearson's chi-squared test for categorical variables. Treatment effects, including clinical response, and the risk of adverse event were calculated as risk ratio (RR) with 95% confidence interval (CI) for dichotomous data. A non-inferiority margin of 10% was used for ECR, based on historical data comparing antibacterial drugs vs nonantibacterial treatments and current guidance from the FDA.[17] The 2-sided 95% confidence intervals (CI) for the differences in ECR and IACR clinical success rates were calculated using the Miettinen and Nurminen method, with stratification.[18] Noninferiority of lefamulin to moxifloxacin was concluded if the lower limit of the 95% CI for the treatment difference was >10%.

3. Results

3.1. The clinical manifestations of patients

Overall, a total of 1289 patients (lefamulin group: 646 and moxifloxacin group: 643) were in this analysis (Table 1, Fig. 1).

Table 1

Demographic characteristics for patients in LEAP 1 and LEAP 2 studies in intention-to-treat population.

Characteristics	No of patients (%)	
	Lefamulin (n = 646)	Moxifloxacin (n = 643)
Mean age, yr	58.9	58.7
Age < 65 yr	378 (58.5)	394 (61.3)
Age 65–74 yr	152 (23.5)	145 (22.6)
Age ≥ 75 yr	116 (18.0)	104 *16.2)
Male sex	377 (58.4)	340 (52.9)
Mean body mass index	26.5	26.4
Race		
White race	513 (79.4)	509 (79.2)
Asian	72 (11.1)	72 (11.2)
American Indian or Alaskan native	24 (3.7)	17 (2.6)
Black	30 (4.6)	34 (5.3)
Others	7 (1.1)	11 (1.7)
Systemic inflammatory response syndrome	621 (96.1)	609 (94.7)
PORT risk		
I	1 (0.2)	2 (0.3)
II	183 (28.3)	190 (29.5)
III	341 (52.8)	334 (51.9)
IV	116 (18.0)	112 (17.4)
V	5 (0.8)	5 (0.8)
Bacteremia	13 (2.0)	12 (1.9)
Met ATS minor severity criteria	85 (13.2)	85 (13.2)

ATS = American Thoracic Society, LEAP = lefamulin evaluation against pneumonia study.

Their mean age was 58.7 years and 40.1% (n = 517) of patients were ≥ 65 years. 55.6% (n = 717) of patients were male and 79.3% (n = 1022) were white race. 1230 patients (95.4%) had systemic inflammation response syndrome and 25 patients (1.9%) had bacteremia. The distribution of PORT risk class was class I: 0.2% (n = 3), II: 28.9% (n – 373), III: 52.4% (n = 675), IV: 17.7% (n = 228) and V: 0.8% (n = 10). Among mITT population (n = 709), *S. pneumoniae* was the most common baseline pathogens (n = 439, 61.9%), followed, *Haemophilus influenzae* (n = 212, 29.9%), *Moraxella catarrhalis* (n = 70, 9.9%), *Mycoplasma pneumoniae* (n = 73, 10.3%), *Legionella pneumophila* (n = 65, 9.2%), *Chlamydophila pneumoniae* (n = 58, 8.2%) and *S. aureus* (n = 33, 4.7%)(Table 2). There was no significant difference in terms of the demographic and baseline characteristics between lefamulin and moxifloxacin group.

3.2. Minimum inhibitory concentrations (MICs)

For *S. pneumoniae* isolates, MIC_{50}/MIC_{90} of lefamulin were 0.25/0.5 μg/ml in both LEAP 1 trial (n = 50) and LEAP 2 trials (n = 80). For macrolide-resistant *S. pneumoniae* isolates, MIC_{50}/MIC_{90} of lefamulin were 0.25/0.5 μg/ml in LEAP 1 trial (n = 12) and 0.25/0.25 μg/mL in LEAP 2 trial (n = 19). For multidrug-resistant *S. pneumoniae* isolates, MIC_{50}/MIC_{90} of lefamulin were 0.25/0.5 μg/ml in LEAP 1 trial (n = 12) and 0.25/0.25 μg/mL in LEAP 2 trial (n = 20). For *S aureus* isolates, MIC_{50}/MIC_{90} of lefamulin were 0.12/0.25 μg/ml in LEAP 1 trial (n = 10) and 0.12/0.12 μg/ml in LEAP 2 trial (n = 14). For 3 MRSA isolates in LEAP 2 trial, MIC of lefamulin was exclusively 0.12 μg/mL. For *H influenzae* isolates, MIC_{50}/MIC_{90} of lefamulin were 1/2 μg/mL in both LEAP 1 trial (n = 11) and LEAP 2 trial (n = 24). For *M catarrhalis* isolates, MIC range of lefamulin were 0.12–0.12 μg/ml in LEAP 1 trial (n = 2) and 0.06 to 0.25 μg/mL in LEAP 2 trial

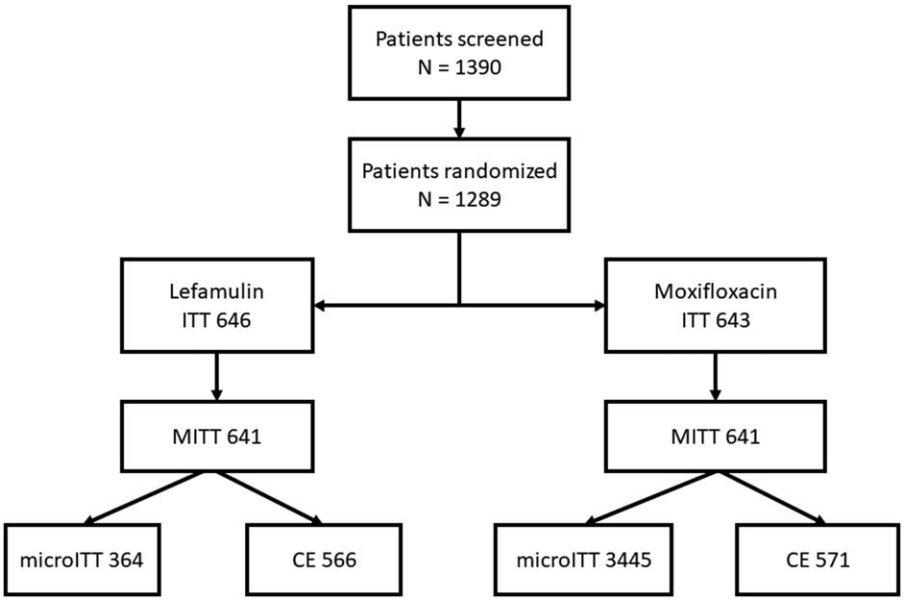

Figure 1. Disposition of patients enrolled in LEAP-1 and LEAP-2. CE = clinically evaluable; ITT = intent-to-treat; MITT = modified ITT; microITT = microbiologic ITT; LEAP = lefamulin evaluation against pneumonia study.

(n = 5). The MIC range of lefamulin against *M. pneumoniae* was ≤0.001–≤0.001 μg/mL in LEAP 1 trial (n = 6) and MIC_{50}/MIC_{90} were ≤0.001/≤0.001 μg/mL in in LEAP 2 trial (n = 11).

3.3. Clinical efficacy

Overall, the early clinical response rate was 89.3% and 90.5% among lefamulin and moxifloxacin group, respectively. Lefamulin was noninferior to moxifloxacin (RR: 0.99, 95% CI: 0.95–1.02, $I^2 = 0\%$; Fig. 2). Regarding nonresponder rate at early clinical assessment, no significant difference was observed between lefamulin and moxifloxacin (9.0% vs 8.1%; RR: 1.11, 95% CI: 0.76–1.63, $I^2 = 11\%$). In terms of clinical response at TOC, no significant difference was observed between the lefamulin and moxifloxacin groups (for MITT population, RR: 0.98, 95% CI: 0.94–1.02, $I^2 = 0\%$; for CE population, RR: 0.96, 95% CI: 0.93–1.00, $I^2 = 0\%$; Fig. 1). Furthermore, the clinical failure rate at TOC remained similar between the lefamulin and moxifloxacin groups (for MITT population, RR: 1.20, 95% CI: 0.90–1.61, $I^2 = 0\%$ and for CE population, RR: 1.40, 95% CI: 0.98–1.99, $I^2 = 0\%$).

Table 2

Common baseline pathogens for patients in LEAP 1 and LEAP 2 studies in microbiological intention-to-treat population.

	No of patients (%)	
Characteristics	**Lefamulin (n = 364)**	**Moxifloxacin (n = 345)**
Streptococcus pneumonia	216 (59.3)	223 (64.6)
Staphylococcus aureus	23 (6.3)	10 (2.9)
Haemophilus influenzae	107 (29.4)	105 (30.4)
Moraxella catarrhalis	45 (12.4)	25 (7.2)
Mycoplasma pneumoniae	39 (10.7)	34 (9.9)
Legionella pneumophila	34 (9.3)	31 (9.0)
Chlamydophila pneumoniae	27 (7.4)	31 (9.0)

LEAP = lefamulin evaluation against pneumonia study.

In the subgroup analysis, the early clinical response rate at early clinical assessment and clinical response rate at TOC of lefamulin was similar to that of moxifloxacin across different subgpopulations (Tables 3 and 4). Lefamulin and moxifloxacin demonstrated high rates of at early clinical assessment and clinical response rate at TOC across all baseline CABP pathogens (Table 5). Lefamulin exhibit similar clinical efficacy to moxifloxacin for most of CABP pathogens, except *Moraxella catarrhalis* (Table 5).

3.4. Risk of adverse events

Overall, lefamulin was associated with a similar risk of AEs as moxifloxacin (TEAE, RR: 1.14, 95% CI: 0.89–1.47, $I^2 = 61\%$; serious AEs, RR: 1.16, 95% CI: 0.72–1.86, $I^2 = 0\%$; treatment related TEAEs, RR: 1.45, 95% CI: 0.77–2.72, $I^2 = 79\%$; treatment related serious AEs, RR: 1.35, 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, $I^2 = 0\%$; and treatment leading to death, RR: 1.37, 95% CI: 0.55–3.39, $I^2 = 0\%$; Fig. 3). However, lefamulin was associated with a higher risk of TEAE in moderate severity than moxifloxacin (RR: 1.41, 95% CI: 1.02–1.96, $I^2 = 79\%$).

For common gastrointestinal adverse event, the risk of nausea and diarrhea was 4.2% and 7.3% among lefamulin group in the pooled analysis. Both were higher than those of moxifloxacin (nausea, RR: 2.03, 95% CI: 1.02–4.03, $I^2 = 6\%$; diarrhea, RR: 1.06, 95% CI: 0. 01–116. 69, $I^2 = 96\%$).

4. Discussion

The integrated analysis of data from 2 RCTs[12,13] with 1289 patients were collated to compare the efficacy and safety of lefamulin and moxifloxacin for treating CABP. In the present study, lefamulin could achieve a similar clinical response as moxifloxacin, which is supported by the following evidence. First, the early clinical response rate for lefamulin was similar to

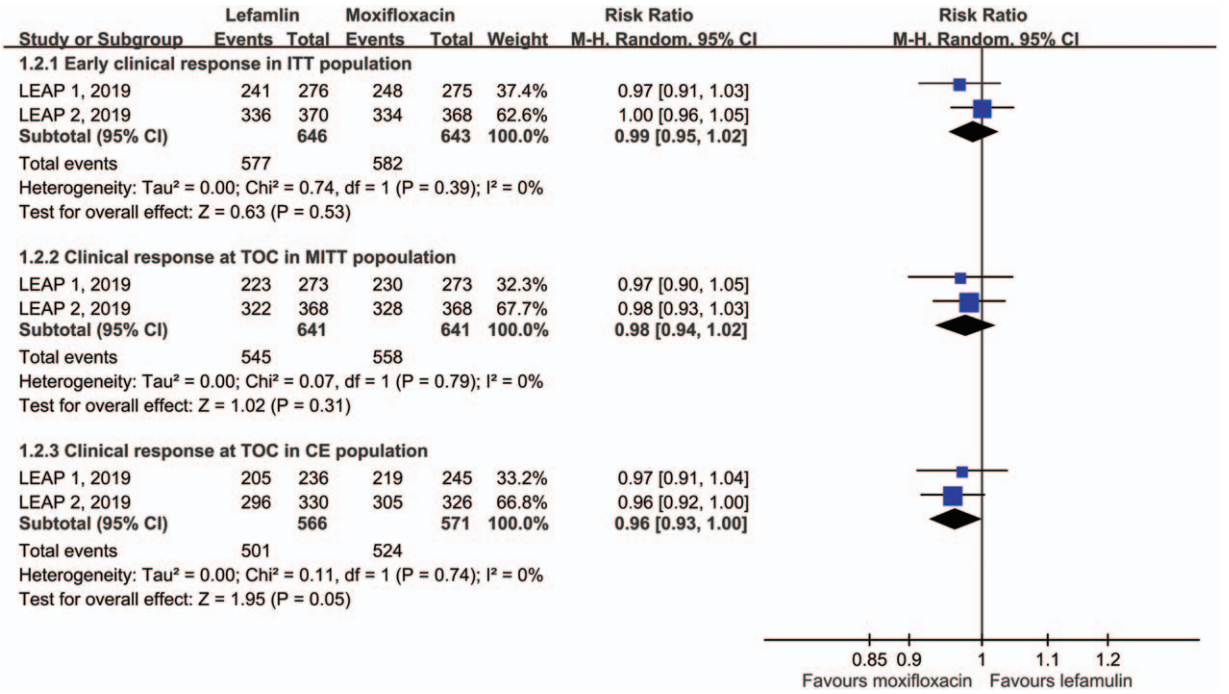

Figure 2. Early clinical response for the intent-to-treat (ITT) population and clinical response at test of cure (TOC) in modified ITT (MITT) and clinically evaluable (CE) populations.

moxifloxacin in the pooled analysis of ITT population. This similarity between lefamulin and moxifloxacin was observed in terms of clinical response rate at TOC among both MITT, and CE population. Second, lefamulin exhibited similar clinical efficacy than moxifloxacin across different age, severity, and various subgroups. Third, the clinical efficacies of lefamulin were similar to those of moxifloxacin across infections caused by different pathogens, including *S pneumoniae*, *S aureus*.

Table 3

Early clinical response in intention-to-treat population by subgroup.

	No. (%)			
	Lefamulin	Moxifloxacin	Risk ratio	95% CI
Sex				
Male	330/377	301/340	0.99	0.92–1.07
Female	247/269	281/303	0.99	0.94–1.04
CURB-65 score				
0	99/111	102/113	0.99	0.91–1.08
1	298/327	291/317	0.99	0.92–1.07
2	149/172	153/174	0.98	0.91–1.07
3	29/34	32/35	0.92	0.78–1.09
4	2/2	4/4	1.00	0.49–2.05
PORT risk class				
I	1/1	2/2	1.00	0.39–2.58
II	168/183	177/190	0.99	0.93–1.04
III	307/341	307/334	0.98	0.93–1.03
IV	97/116	93/112	1.01	0.90–1.13
V	4/5	3/5	1.32	0.22–7.92
Met SIRS criteria				
Yes	553/621	550/609	0.99	0.95–1.03
No	24/25	32/34	1.03	0.92–1.15
Bacteremia				
Yes	8/13	10/12	0.78	0.46–1.31
No	569/633	572/631	0.99	0.96–1.03
Prior antibiotic use				
Yes	133/147	129/145	1.02	0.94–1.09
No	444/499	453/498	0.98	0.94–1.02

CI = confidence interval.

Table 4

Clinical response in modified intention-to-treat population by subgroup.

	No. (%)			
	Lefamulin	Moxifloxacin	Risk ratio	95% CI
Sex				
Male	309/374	285/339	0.99	0.92–1.05
Female	236/267	273/302	0.98	0.92–1.03
CURB-65 score				
0	97/110	99/113	1.05	0.86–1.28
1	280/324	280/316	0.98	0.93–1.04
2	140/171	143/173	1.00	0.90–1.10
3	26/34	32/35	0.84	0.67–1.04
4				
PORT risk class				
I	1/1	1/2	1.50	0.38–6.00
II	157/183	175/190	0.93	0.87–1.00
III	294/337	286/333	1.02	0.96–1.08
IV	89/115	93/111	0.93	0.81–1.05
V	4/5	3/5	1.32	0.22–7.92
Met SIRS criteria				
Yes	523/616	526/607	0.98	0.94–1.03
No	22/25	32/34	0.94	0.82–1.11
Bacteremia				
Yes	4/13	9/12	0.53	0.24–1.21
No	541/628	549/629	0.99	0.95–1.03
Prior antibiotic use				
Yes	123/146	119/143	1.02	0.92–1.12
No	422/495	439/504	0.98	0.93–1.03

CI = confidence interval.

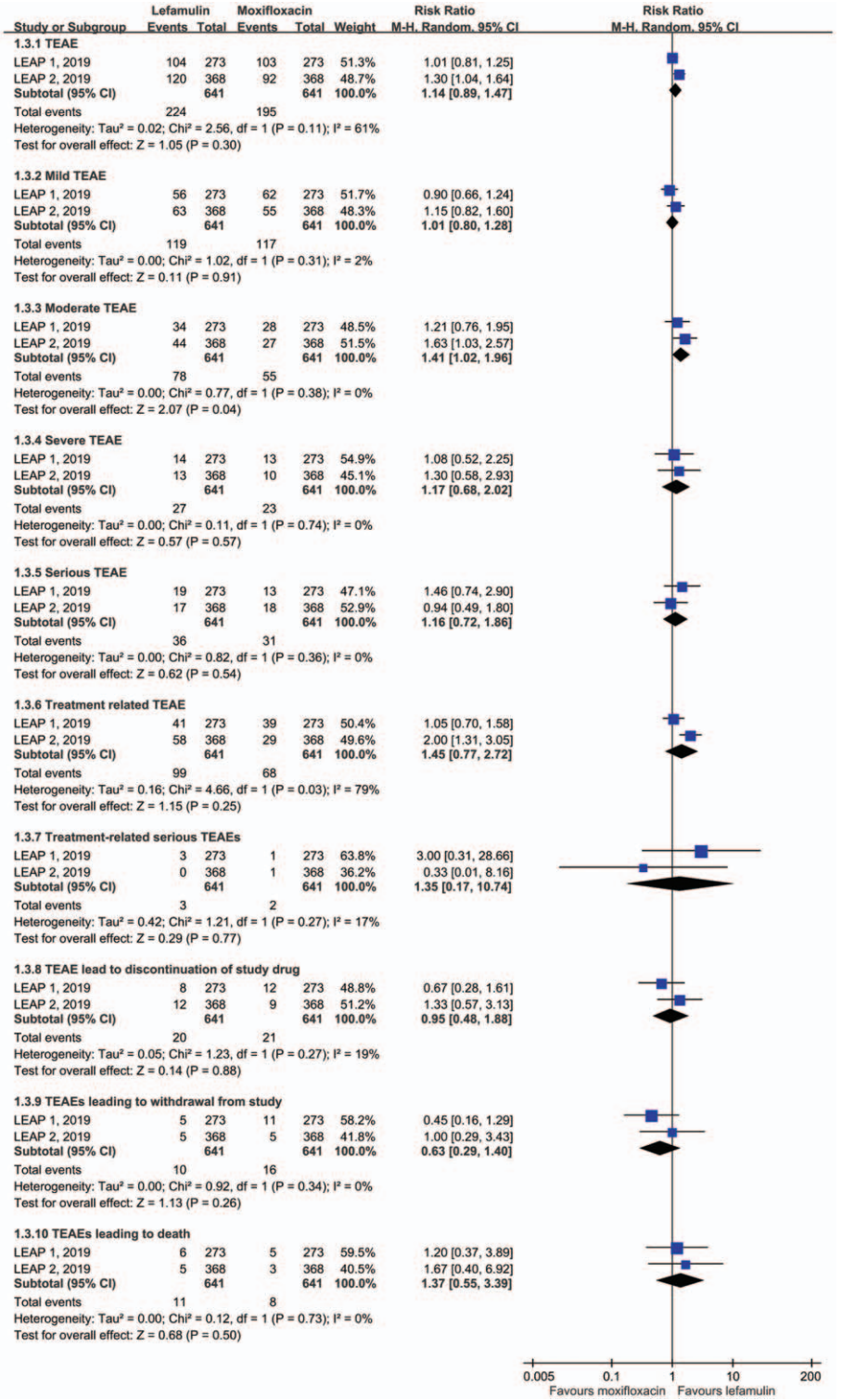

Figure 3. Risk of adverse event.

H inlfuenzae, M pneumoniae, L pneumophila and *C pneumoniae*. The only exception was *M catarrhalis*, in which lefamulin exhibit a lower clinical response at TOC than moxifloxacin. In summary, all these findings indicate that lefamulin can be as effective as moxifloxacin for treating CABP.

In this study, we also found the potent in vitro activity of lefamulin against CABP pathogens according to the MIC tests. For key CABP pathogens, including *S pneumonia, S aureus, H influenzae, M catarrhalis,* and *Mycoplasma pneumoniae,* the MIC value of lefamulin remain low in both LEAP 1 and LEAP 2 trials.[12,13] Even for antibiotic-resistant organisms, such as MDR *S. pneumoniae* and MRSA, lefamulin still exhibit good in vitro activity. In fact, several global investigations have revealed that lefamulin exhibited potent in vitro activity against key CABP

Table 5

Early clinical response for the intent-to-treat (ITT) population and clinical response at test of cure in modified ITT by baseline pathogen.

	Early clinical response				Clinical response			
	No. (%)				No. (%)			
	Lefamulin	Moxifloxacin	Risk ratio	95% CI	Lefamulin	Moxifloxacin	Risk ratio	95% CI
Streptococcus pneumonia	192/216	206/223	0.96	0.91–1.02	184/216	193/223	0.98	0.91–1.06
Staphylococcus aureus	23/23	10/10	1.00	0.83–1.20	20/23	9/10	0.99	0.74–1.32
Haemophilus influenzae	97/107	98/105	0.97	0.90–1.05	95/107	88/105	1.06	0.95–1.18
Moraxella catarrhalis	41/46	22/22	0.92	0.80–1.05	37/46	22/22	0.83	0.70–0.98
Mycoplasma pneumoniae	3639	32/34	0.99	0.89–1.10	35/39	33/34	0.94	0.83–1.06
Legionella pneumophila	29/34	28/31	0.94	0.78–1.14	27/34	26/31	0.95	0.75–1.19
Chlamydophila pneumoniae	25/27	30/31	0.95	0.83–1.10	20/27	23/31	0.96	0.71–1.29

CI = confidence interval, ITT = intent-to-treat.

pathogens as well as was active against antibiotic-resistant organisms.[10,11,19] For *S pneumoniae* isolates, lefamulin exhibited MIC_{50} and MIC_{90} values of 0.12 and 0.25 μg/mL, respectively, against a total of 822 strains collected in United State.[19] Even for MDR *S. pneumoniae* isolates, the MIC_{50} and MIC_{90} of lefamulin was only 0.12 and 0.25 μg/mL, respectively.[19] For *Mycoplasma pneumoniae* isolates, all MICs of lefamulin against 18 macrolide-susceptible and 42 macrolide-resistant strains were $\leq$0.008 μg/mL and lefamulin had lowest MIC_{90} (0.002 μg/mL) for macrolide-resistant strains among all tested agents including azithromycin, erythromycin, tetracycline, doxycycline, and moxifloxacin.[11] In a global surveillance of 8595 commonly encountered pathogens causing CABP, lefamulin can inhibited 99.2% of all isolates tested, including 100% of *S pneumoniae* isolates, 99.8% of *S aureus* isolates, 93.8% of *H influenzae* isolates, and 100% of *M catarrhalis* isolates, using the susceptible breakpoint of MIC $\leq$1 μg/mL.[10] For multidrug-resistant and extensively drug-resistant *S pneumoniae* strains, all $MIC_{50/90}$ values were only 0.06/0.12 μg/mL. The $MIC_{50/90}$ value of lefamulin against MRSA were 0.06/0.12 μg/mL. Therefore, these findings can help support the use of lefamulin for treating CABP.

Finally, the risk of AEs for lefamulin was assessed. Lefamulin was associated with higher risk of gastrointestinal AE than moxifloxacin, especially for oral form. In LEAP 2 trial, only oral lefamulin was used and the gastrointestinal-related AE – mostly diarrhea, occurred in 17.9% of patients. In LEAP 1 trial, gastrointestinal events more developed during oral than IV treatment with lefamulin (7.7% vs 3.7%). Thus, it reminds us the importance of closely monitoring gastrointestinal intolerance during the use of oral lefamulin. Although lefamulin carried higher risk of moderate TEAE than moxifloxacin, lefamulin had a similar risk of AEs in TEAEs, serious AEs, treatment related TEAE, treatment related serious AE, treatment discontinuation/withdraw due to TEAEs, and treatment leading to death when compared with moxifloxacin. All these findings indicated that lefamulin was found to be as tolerable as moxifloxacin.

This study has some limitations. First, we could not assess the association between in vitro activity and clinical response for each specific pathogen due to the unavailability of data. Second, we did not evaluate the cost-effectiveness of lefamulin in this study. The cost of lefamulin is several-fold more than moxifloxacin.[20] Third, neutrophil biology and inflammation plays important role in pneumonia,[21] however, these 2 studies did not assess this issue. Finally, all of the data were obtained from the published articles only and that participant level data were not available. Although this issue could limit the findings of this integrated analysis, this study combined LEAP 1 and LEAP 2 to allow subgroup analysis and confirm the results of each individual study in the combined analysis. However, further study is warranted to clarify these above issues.

In conclusion, clinical efficacy and tolerability for lefamulin in the treatment of CABP were similar to those for moxifloxacin.

Author contributions

Conceptualization: Hung-Jen Tang, Chih-Cheng Lai.
Data curation: Hung-Jen Tang, Jui-Hsiang Wang.
Formal analysis: Jui-Hsiang Wang.
Writing – original draft: Hung-Jen Tang, Chih-Cheng Lai.

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