International Journal of Research in Medical Sciences
Saseedharan S et al. Int J Res Med Sci. 2021 Oct;9(10):2933-2939
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20213685

Original Research Article

Efficacy and safety of intravenous and/or oral levonadifloxacin in the management of secondary bacterial pulmonary infections in COVID-19 patients: findings of a retrospective, real-world, multi-center study

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Received: 24 August 2021
Revised: 08 September 2021
Accepted: 09 September 2021

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ABSTRACT

Background: Owing to dysregulated immune response, secondary bacterial pulmonary infections involving both gram-positive and gram-negative pathogens are common in COVID-19 patients and are often associated with higher mortality. This is a first ever report on the safety and efficacy of levonadifloxacin in the treatment of secondary bacterial pulmonary infections in patients with COVID-19 pneumonia.
Methods: This multi-center, retrospective, post-marketing and real-world study assessed the safety and efficacy of IV and/or oral levonadifloxacin in the treatment of bacterial infections encountered in COVID-19 patients. Data for 154 male/female patients above 18 years of age who received levonadifloxacin (injectable and/or oral) was collected from 44 participating sites. Study outcomes were the clinical and microbial success at the end of therapy. Safety was assessed based on clinical and laboratory adverse events.
Results: Among the 154 patients assessed, 121 (78.6%) were males and 142 (92.2%) were hospitalized. Majority of the patients (119) received all-IV therapy while 11 patients were prescribed with IV followed by oral regimen. All-oral therapy was received by 24 patients. The most common co-morbid conditions were diabetes (19.6%) and hypertension (19.2%). Post-treatment with levonadifloxacin, clinical and microbial success rates were 96.8% and 97.0% respectively.
Conclusions: Levonadifloxacin showed promising safety and efficacy when used as IV and/or oral therapy for the treatment of secondary bacterial pulmonary infections in COVID-19 patients. Clinically relevant features of levonadifloxacin such as availability of both IV and oral options, broad spectrum coverage and reassuring safety in patients with significant co-morbidities could help simplify the management.
Trial registration no. CTRI/2020/09/028152 [Registered on: 30/09/2020].

Keywords: COVID-19, Levonadifloxacin, Secondary bacterial infections, Real world study

INTRODUCTION

COVID-19 pandemic has spread from its epicenter in Wuhan, China to all over the world. Despite most of the patients infected with the SARS-CoV-2 show self-limiting progression of symptoms, a minor proportion develops severe pneumonia and requires the supplemental oxygen. One third of these pneumonia patients have been reported to progress to critical illness with acute respiratory distress syndrome (ARDS), hypoxemic respiratory failure, with some of the cases showing multi-organ failure requiring a mechanical ventilation.[1,2]

Post-hospitalization, with progression of COVID-19 associated pneumonia, co-infection of various bacterial pathogens and fungi has been reported, a scenario similar to respiratory illness caused by other viruses, such as seasonal/pandemic influenza, Middle East respiratory syndrome corona virus (MERS-CoV) and SARS-CoV-1.[3,4] Secondary bacterial pulmonary infections are predominantly observed in critically-ill hospitalized COVID-19 patients.[5] Most secondary bacterial infections (infections occurring 48 hours after hospital admission) occur within the first 14 days of hospital admission.[6] Also, in the past, co-infection in COVID-19 patients has been associated with more severe outcomes in pandemic and seasonal influenza.[7] A meta-analysis reports a prevalence of co-infection in up to 50% among non-survivors affected by COVID-19.[8] Vijay et al reported an overall 3.6% of secondary bacterial or fungal infections in hospitalized COVID-19 patients in India. The most common bacterial co-pathogens involved were *Klebsiella pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumonia, Legionella pneumophila, Acinetobacter baumannii, Streptococcus pneumonia* and *Staphylococcus aureus*.[9]

Due to the possibility of polymicrobial infections involving multidrug-resistant bacterial pathogens in patients with COVID-19, the choice of appropriate antibiotic treatment is highly challenging. For instance, prevalence of methicillin-resistant *S. aureus* (MRSA) has been reported to be in excess of 40 percent and to make the situation complicated nearly over 90 percent of MRSA also demonstrate a high-level of quinolone resistance.[10,11] Prevalence of vancomycin-intermediate *Staphylococci* also hovers around 10 percent, despite the challenges in detecting this resistance mechanism.[12] Involvement of MDR *Staphylococci* without the knowledge of underlying resistance mechanism (such as VISA, MRSA or quinolone-resistant *Staphylococci*) as a secondary bacterial infection in COVID-19 patients impedes the empiric use of glycopeptide (such as vancomycin, teicoplanin or daptomycin) and quinolone class of antibiotics (such as ciprofloxacin, levofloxacin and moxifloxacin). Moreover, glycopeptides are not suitable in clinical situations suspected or confirmed to involve gram-negative infections. Though linezolid is active against MRSA and QRSA, it is marred by therapy-duration limiting toxicity as well as particularly myelosuppression, which could further complicate the clinical situation in COVID-19 patients with several presenting with pre-existing immuno-suppression. Such gaps in the coverage of older antibiotics compel clinicians to deploy a cocktail of antibiotics which pose challenges of dose adjustments, enhanced risk of toxicity, and drug-drug interaction, thus further complicating the management of COVID-19 patients. In view of this, there is an urgent need of the simplified antibiotic options which could be used in polymicrobial etiology with an ability to overcome the majority of resistance mechanisms.

Levonadifloxacin is a recently approved antibiotic for clinical use with a broad-spectrum activity and is available as both oral and injectable formulation in India. It's activity spectrum encompasses a range of gram-positive organisms like *Staphylococcus aureus* (methicillin-resistant, methicillin-susceptible, quinolone-resistant, quinolone-susceptible isolates), *Streptococcus pyogenes, Enterococcus faecalis, Streptococcus dysgalactiae spp. dysgalactiae*, as well as all the pathogens involved in community-acquired bacterial pneumonia such as *S. pneumoniae, Haemophilus influenzae, M. catarrhalis, S. pyogenes*, and atypical respiratory pathogens such as *Legionella spp.*, *Chlamydia spp.* and *Mycoplasma spp*. It has also been reported to be active against quinolone-susceptible Gram-negative bacteria and anaerobes.[13,14] Due to high concentrations in lungs, and potent intracellular activity against entire range of potential respiratory pathogens, levonadifloxacin could be well suited for the treatment of respiratory infections caused by extracellular and intracellular pathogens, especially in COVID-19.[15] Also, the emerging clinician-friendly safety profile of levonadifloxacin even in patients with multiple co-morbidities is expected to simplify the treatment of secondary bacterial pulmonary infections in patients with COVID-19 and co-morbidities.

This study aims to capture the efficacy and safety of levonadifloxacin as an injection and/or oral for treatment of bacterial pulmonary infections in patients with SARS-CoV-2 infection.

METHODS

Setting

The data presented here is part of a large multicenter, retrospective, post-marketing, real-world, observational study (PIONEER study) conducted for the assessment of safety and efficacy of levonadifloxacin in India. The outcome with levonadifloxacin use in a subset of COVID-19-confirmed patients, treated in 40 hospitals (all hospital names are mentioned in acknowledgement section) between period of July 2020 to March 2021, across India is reported.

Ethics

The study documents were reviewed and approved by the institutional ethics committee (IEC) of D. Y. Patil university school of medicine, Navi Mumbai (DYP/IEC/06-019/2020). The study was conducted in accordance with the principles of declaration of Helsinki (World medical association) and good clinical practice (GCP) guidelines issued by the ICMR and CDSCO, govt. of India. This being a retrospective study, patient consent was obtained wherever possible, and strict confidentiality was maintained for patient's identity.

Study participants

Male or female patients above 18 years of age, diagnosed or suspected with secondary bacterial pulmonary infections in COVID-19 and received levonadifloxacin (oral or injectable) (number of patients were 154) were included. The definition of a confirmed case of COVID-19 was in accordance with world health organization interim guidance. The diagnosis of COVID-19 was confirmed by a positive result of real-time reverse-transcription polymerase chain reaction (RT-PCR) for respiratory specimens (throat and/or nasopharyngeal swabs). Data was collected and recorded in a study specific data capture format at forty-four participating sites. Patient information such as clinical condition on admission, comorbidities, complications, and details of other treatment (including antimicrobial agents) received was collected. Microbial testing data was collected wherever available. This being an observational study, there were no pre-defined treatment protocols as well as the patients were treated at the discretion of the clinicians.

Study outcomes

The study outcomes were reported by i) clinical success and ii) microbial success at the end of therapy. Clinical success is defined as the resolution or improvement in signs and symptoms without the need of additional antibiotic treatment. Clinical failure is defined as persistence or worsening of signs/symptoms, the need for additional antibiotic, new pulmonary infection, progression of the chest radiograph, or death due to pneumonia. Microbial success is defined as absence of organism in the follow-up microbial testing in those patients where organisms were detected at baseline, or a negative follow-up microbial testing. Clinical improvement was defined as improvement in clinical signs and symptoms from the baseline.

The safety was assessed using the clinical and laboratory adverse events documented. Additionally, global assessments were made by the treating investigator for each patient for efficacy and safety based on a 5-point Likert scale of excellent, very good, good, satisfactory and poor.

Statistical analysis

This being an observational study, there is no study hypothesis, and therefore no statistical testing was done. Measurement data are presented as means and standard deviation (SD), whereas categorical data is presented as numbers with percentages. $P<0.05$ was considered statistically significant.

RESULTS

Of the 154 patients, 121 (78.6%) were males and 33 (21.4%) were females with a median age of 60.50 years (range 28 to 88 years). Table 1 presents the demography and duration of levonadifloxacin therapy received by the patients. Most of the patients (n=119, 77.3%) received IV levonadifloxacin, 24 (15.6%) patients received oral therapy and 11 (7.1%) received IV therapy followed by switchover to oral levonadifloxacin. The most common comorbid conditions were diabetes (19.6%) and hypertension (19.2%). Other comorbidities were ischemic heart disease (5.2%), thyroid disorders (2.6%), renal disorders (1.9%), malignancy (3.2%), respiratory disorder (1.3%) and the seizure disorder (1.3%).

Table 2 presents the systems involved and complications reported in patients with COVID-19. Complications were reported in 33 (23.7%) patients with systemic inflammatory response syndrome (SIRS) being the common complication. Concomitant drugs other than study antimicrobial agents (AMA) used were anticoagulants (16.2%), oral hypoglycemic agents (10.4%), corticosteroids (7.8%), antihypertensive (3.2%) and other drugs (16.2%). About 109 patients received concomitant AMAs with 101 (65.6%) receiving only one AMA along with levonadifloxacin, whereas 8 (5.2%) patients received two additional AMAs. The common AMAs used along with levonadifloxacin were meropenem/imipenem/carbapenem (19.5%), remdesivir (16.2%), polypeptides (1.9%), macrolides (1.9%), beta-lactams (1.3%), antifungals (3.9%) and 29.2% received other AMAs.

Table 3 presents the results of microbial investigation carried out in 88 patients on hospitalization. Culture report was positive in 45.5% patients; 20.5% and 18.2% of gram-positive (*Staphylococcus aureus*, MRSA, *Enterococcus)* and gram-negative (*Klebsiella and Pseudomonas aeruginosa)* cultures respectively, were observed.

Table 4 presents the clinical (96.8%) and microbial (97.0%) success rates. Figure 1 presents the global assessments for efficacy (Excellent-44.2%, very good-28.6%, good-22.1%, satisfactory-5.2% and poor-0.0%) and safety (Excellent-42.9%, very good-28.6%, good-25.3%, satisfactory-3.2% and poor-0.0%) at end of therapy.

No adverse events were reported in the patients' records.

Table 1: Demography and duration of levonadifloxacin therapy, (n=154).

Levonadifloxacin		Age (years)	BMI (kg/m^2)	Duration of therapy (days)
IV, (n=119)	Mean	61.55	25.66	7.28
	SD	12.02	3.76	3.73
	Median	62	25.21	7.00
	Range	28-88	19.72-46.87	2-32
Oral, (n=24)	Mean	58.96	25.892	6.6
	SD	11.61	3.83	1.79
	Median	59	25.03	6.00
	Range	35-75	18.43-32.69	5-11
IV followed by oral, (n=11)	Mean	58.18	25.44	13.38
	SD	11.65	4.11	3.936
	Median	56	24.46	13.00
	Range	42-80	20.45-3.06	8-21
All patients, (n=154)	Mean	60.91	25.68	7.53
	SD	11.91	3.77	3.29
	Median	60.5	25.19	7.00
	Range	28-88	18.43-46.87	2-21

Demographic details of age and body mass index (BMI) are mentioned for IV levonadifloxacin, oral levonadifloxacin, IV followed by oral levonadifloxacin and all patients. Duration of levonadifloxacin therapy in days is measured for IV levonadifloxacin, oral levonadifloxacin, IV followed by oral levonadifloxacin and all patients.

Table 2: Other systems involved and complications of COVID-19, (n=154).

Other systems involved			Complications		
	No.	**Percentage (%)**		**No.**	**Percentage (%)**
Abdominal	3	1.9	SIRS	15	9.7
Cardiovascular	2	1.3	Septic shock	6	3.9
Skin/Soft tissue	16	10.4	Multi Organ Failure	7	4.5
Pelvic	0	0.0	Renal impairment	11	7.1
Neurological/Meningeal	3	1.9	Hepatic Impairment	1	0.6
Retroperitoneal	0	0.0	Thrombocytopenia	3	1.9
Other systems involved	7	4.5	Other complications	34	24.3

Other systems involved and complications of COVID-19 are mentioned in numbers and percentage of n=154. SIRS is systemic inflammatory response syndrome.

Table 3: Microbial testing results at baseline, (n=88).

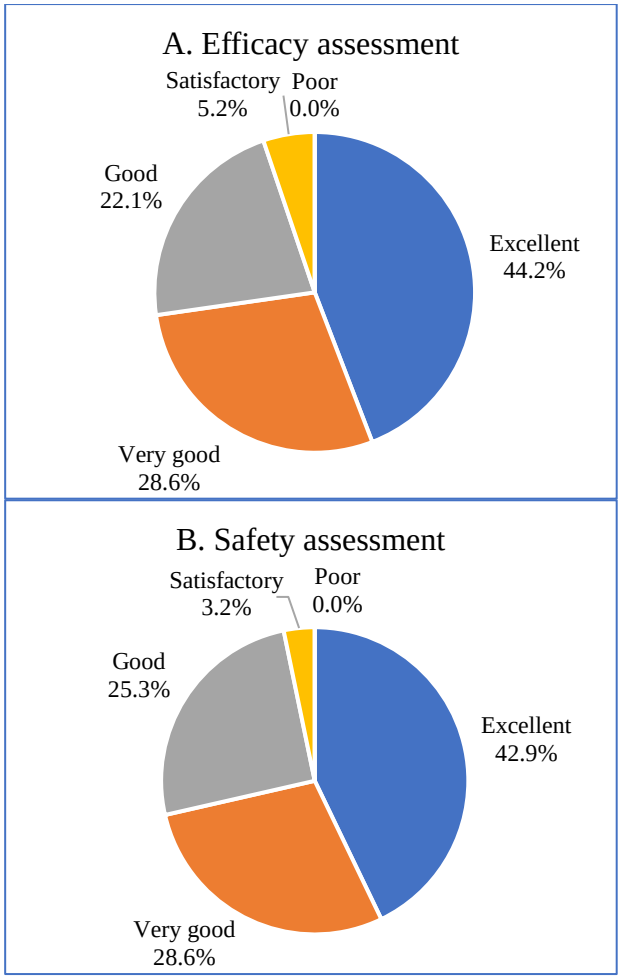
Organisms detected	No.	Percentage (%)
Gram-positive	18	20.5
Gram-negative	16	18.2
Atypical organisms	3	3.4
Anaerobic organisms	3	3.4
Negative culture	48	54.5

Microbial testing results at baseline are mentioned in group of organisms detected in numbers and percentage of n=88.

Table 4: Study outcomes at the end of therapy.

Variables	Clinical success		Microbial success	
	N	**Percentage (%)**	**N**	**Percentage (%)**
IV	114/119	95.8	26/27	96.3
Oral	24/24	100	6/6	100
IV followed by oral	11/11	100	-	-
All patients	149/154	96.8	32/33	97

Study outcomes at the end of therapy are mentioned in clinical success, (n=154) and microbial success, (n=33) as numbers and percentage for IV levonadifloxacin, oral levonadifloxacin, IV followed by oral levonadifloxacin and all patients.



(A) Efficacy assessment at end of therapy made by treating investigator based on five-point scale of excellent, very good, good, satisfactory and poor. (B) Safety assessment at end of therapy made by treating investigator based on five-point scale of excellent, very good, good, satisfactory and poor.

Figure 1 (A and B): Global assessment at end of therapy, (n=154).

DISCUSSION

Empirical antibiotic therapy in hospitalized COVID-19 patients is necessitated as many reports across the globe have established the occurrence of secondary bacterial infections in such patients thereby complicating the clinical prognosis. Levonadifloxacin is a recently introduced novel antibiotic with a broad-spectrum antibacterial activity. In particular, it is highly active against Gram-positive pathogens including MRSA and antibiotic-resistant community respiratory pathogens. The regulatory approval for levonadifloxacin was based on a successful, well-controlled, phase 3, randomized clinical trial. After its launch, various post-marketing studies are underway. The present investigation was undertaken retrospectively to assess the safety and efficacy of levonadifloxacin administered to a subset of COVID-19 confirmed patients.

Occurrence of secondary bacterial infections is predisposed by the severity of COVID-19 and severe disease patients have greater prevalence of secondary bacterial infections.[16] Critically-ill patients have been reported to have the highest proportion of secondary pulmonary infections (34.5%) compared to moderately ill (3.9%) COVID-19 patient.[17] This high rate of secondary pulmonary infections occurs despite a majority of critically ill patients receive antibiotics. Lansbury et al reported a higher proportion of secondary bacterial infections in patients admitted to ICU.[18] Our study also had most of the patents hospitalized with moderate to severe disease thus predisposing them for secondary bacterial infections. In a systematic review involving 5047 hospitalized patients with COVID-19, Chong et al reported the incidence of secondary bacterial pulmonary infection as 16% (4.8% to 42.8%).[7] Dhesi et al also reported similar panel of bacteria, *K. pneumoniae* was again the most frequent organism followed by *S. aureus* in secondary bacterial pneumonia in COVID-19 patients.[17] Another study from China by Zhu et al reports *S. pneumoniae* followed by *K. pneumonia* and *H. influenzae* to be the most common bacteria causing secondary bacterial pneumonia in COVID-19.[20]

There were records for 154 COVID-19 confirmed patients treated with IV or/and oral levonadifloxacin for suspected or confirmed secondary bacterial pulmonary infections. Majority of the patients were males which is consistent with reported gender differences in the epidemiology of COVID-19. Since most of the patients were hospitalized, barring 24 patients, all were instituted with IV regimen of levonadifloxacin with a 7 days median duration of therapy. The switch to oral therapy was reported for 11 patients. Interestingly, 24 patients were administered all-oral therapy. The convenience of being able to initiate and continue oral therapy with Levonadifloxacin is a result of excellent oral bioavailability of its alanine prodrug (alalevonadifloxacin) at about 90% bioavailability.[16] It should be noted that, levonadifloxacin is the lone available oral option with comprehensive coverage (>90% susceptibility) of gram-positive pathogens including MRSA; bestowed with safety features enabling longer duration of therapy.[21,22] With respect to comorbidities, apart from SIRS, patients under assessment were reported to have several complications which included sepsis. In such scenarios, a potent bactericidal antibiotic such as levonadifloxacin could be an ideal choice as compared to a slowly cidal or bacteriostatic antibiotic agent.[16]

In general, although there is a fulminant bacterial infection in the lungs, diagnosis is a challenge and therefore, empirical antibiotic treatment is initiated at clinicians' judgement for a likely bacterial involvement. In the present investigation, there were 88 patients for whom, microbial diagnosis was undertaken. Negative culture rate was 54.5% (48/88) and among the positive-cultures, gram-positive pathogens like *Staphylococcus*

aureus, MRSA, *Enterococcus* were common, closely followed by gram-negative pathogens like *Klebsiella and Pseudomonas aeruginosa*. The recently published studies that examined the microbiology of secondary bacterial infections in COVID-19 cases showed involvement of a broad range of community and hospital-acquired pathogens. The observation in the present study is in agreement with these published findings.[7,17-21]

In this study, the clinical success rate of levonadifloxacin was >90% irrespective of IV or oral regimen, which was comparable to pivotal phase 3 trial in which levonadifloxacin IV and oral regimens demonstrated 91% and 95.2% clinical cure rates. Furthermore, no AEs were encountered for the evaluated 154 patients.

The observed efficacy of levonadifloxacin for pulmonary infections is attributable to several clinically-relevant features such as i) higher lung exposures, ii) bactericidal activity, iii) intracellular activity, iv) broad-spectrum coverage of respiratory pathogens and v) immunomodulatory activity.[16,22] It should be interesting to note that current therapeutic options lack levonadifloxacin-comparable broader antimicrobial coverage as well as remarkable safety profile through IV and oral administration.

In light of the fact that COVID-19 patients may present with immunosuppression, anti-inflammatory activity of levonadifloxacin involving inhibition of pro-inflammatory cytokines, as established through nonclinical studies, could potentially offer clinical benefits in terms of early resolution of symptoms and restricting the progression towards severe respiratory disease.[23]

The main strength of our study is that it includes data on real-word scenario for COVID-19 management from hospitals across the country and thus, this study provides insights on the use of AMAs in COVID-19 patients. Also, very few studies are reported from India regarding use of antibiotic in COVID-19. The study, however, has a few limitations. Due to the retrospective study design, there was no study monitoring and there is no control on the different confounding factors. Also, our study is restricted to a short-term follow-up limited till the patients were discharged from hospital.

CONCLUSION

Clinically relevant features of levonadifloxacin such as availability of both IV and oral option, lack of drug-drug interaction, freedom from dose adjustments in renal and hepatically impaired patients, broad spectrum coverage and reassuring safety in patients with significant comorbidities could help simplify the management of secondary bacterial pulmonary infections in COVID-19. Further, immunomodulatory activity of levonadifloxacin is expected to provide additional clinical benefits. In sum, levonadifloxacin is an important addition to our armamentarium, specifically for the treatment of COVID-19 patients with secondary bacterial pulmonary infections.

ACKNOWLEDGEMENTS

We would like to thank all the investigators for their valuable contribution in the study: Dr. Abizer Manked (Saifee hospital, Mumbai), Dr. Pankaj Joshi (Marudhar hospital, Jaipur), Dr. Kapil Zirpe (Ruby hall clinic, Pune), Dr. Ravi Dosi (SAIMS hospital, Indore), Dr. Sajal Mahajan (D. Y. Patil hospital, Navi Mumbai), Dr. Sampat Shah (Bhatia hospital, Mumbai), Dr. Sandeep (Malla Reddy hospital, Hyderabad), Dr. Sudershana Patil (Wockhardt hospital, Pune), Dr. Suresh Ade (Apollo hospital, Navi Mumbai), Dr. Tyron Fernandis (Sterling hospital, Baroda), Dr. Alok Joshi (Max hospital, Delhi), Dr. Chirag Chatwani (Ashirwad Infectious Disease Clinic, Surat), Dr. Dinakaran (Life Line hospital, Chennai), Dr. Hemant Thakkar (Breach Candy hospital, Mumbai), Dr. Hiten Areliya (Prime Infectious Disease Clinic, Baroda), Dr. Jay Kothari (Apollo hospital, Ahmedabad), Dr. Raviraj Gohil (Rhythem hospital, Baroda), Dr. Sanjay Vaidya (Hinduja hospital, Mumbai), Dr. Achint Narang (Alchemist hospital, Chandigarh), Dr. Avinash (Lotus Cure hospital, Hyderabad), Dr. Deepak Bansal (Bombay hospital, Indore), Dr. K Kurmanandh (Vijetha hospital, Vishakapatnam), Dr. Lipika Parulekar (Holy Family hospital, Mumbai), Dr. N Kanodia (Sheker hospital, Lucknow), Dr. Naval Chandra (NIMS, Hyderabad), Dr. Prashant Walse (Asian City Care, Aurangabad), Dr. Pratik Savaj (Private Clinic, Surat), Dr. Reshma Tiwari (Artemis hospital, Gurugram), Dr. Vasant Nagvekar (Lilavati hospital, Mumbai), Dr. Yatin Mehta (Medanta hospital, Gurugram), Dr. Abhijeet Khandelwal (Gokuldas hospital, Indore), Dr. Anand Sanghi (Choitram hospital, Indore), Dr. Ashish Jain (M.G. hospital, Jaipur), Dr. Madhusudan Jaju (Care Nampally, Hyderabad), Dr. Manoj Mehta (Sterling hospital, Baroda), Dr. Prakash Chouhan (Bodyline hospital, Ahmedabad), Dr. Pramod Kadam (Ruby Hall Clinic, Pune), Dr. Prashant Borade (Global hospital, Mumbai), Dr. Prashant Kumar Singh (Ruban hospital, Patna), Dr. Ratan Jha (Virinchi hospital, Hyderabad).

Funding: The study was sponsored by Wockhardt Ltd.
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report

of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA, 2020;323(13):1239-42.
3. Zahariadis G, Gooley TA, Ryall P, Hutchinson C, Latchford MI, Fearon MA et al. Risk of ruling out severe acute respiratory syndrome by ruling in another diagnosis: variable incidence of atypical bacteria coinfection based on diagnostic assays. Can Resp J. 2006;13(1):17-22.
4. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, AL-Rabiah FA, Al-Hajjar S, Al-Barrak A et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. Lancet Infect Dis. 2013;13(9):752-61.
5. Chong WH, Saha BK, Ramani A, Chopra A. State-of-the-art review of secondary pulmonary infections in patients with COVID-19 pneumonia. Infection. 2021;11:1-15.
6. Khurana S, Singh P, Sharad N, Kiro VV, Rastogi N, Lathwal A et al. Profile of co-infections and secondary infections in COVID-19 patients at a dedicated COVID-19 facility of a tertiary care Indian hospital: Implication on antimicrobial resistance. Indian J Med Microbiol. 2020;39(2):147-53.
7. Joseph C, Togawa Y, Shindo N. Bacterial and viral infections associated with influenza. Influenza Other Respir Viruses. 2013;7(2):105-13.
8. Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: The need for combination therapy withnon-anti-SARS-CoV-2 agents? J Microbiol, Immunol Infect. 2020;53:505-12.
9. Chen, X, Liao, B, Cheng, L, Peng X, Xu X, Li Y et al. The microbial coinfection in COVID-19. Appl Microbiol Biotechnol. 2020;104:7777-85.
10. Indian Network for Surveillance of Antimicrobial Resistance (INSAR) group, India. Methicillin resistant *Staphylococcus aureus* (MRSA) in India: prevalence and susceptibility pattern. Indian J Med Res. 2013;137(2):363-369.
11. Gade ND, Qazi MS. Fluoroquinolone Therapy in *Staphylococcus aureus* Infections: Where Do We Stand? J Lab Physicians. 2013;5(2):109-12.
12. Selvabai AP, Abdul Sattar SB, Jayaraman P, Shanmugam P. Detection and Characterization of Heteroresistant Vancomycin Intermediate *Staphylococcus aureus* (hVISA) using Phenotypic and Genotypic Methods. J clin diagnostic res. 2019;13(5):DC01-5.
13. Bhatia A, Mastim M, Shah M, Gutte R, Joshi P, Kumbhar D et al. Efficacy and Safety of a Novel Broad-Spectrum Anti-MRSA Agent Levonadifloxacin Compared with Linezolid for Acute Bacterial Skin and Skin Structure Infections: A Phase 3, Openlabel, Randomized Study. J Assoc Physicians India. 2020;68(8):30-36.
14. Bakthavatchalam YD, Rao SV, Isaac B, Mahesh A, Nambi S, Swaminathan S et al. A comparative assessment of clinical, pharmacological and antimicrobial profile of novel anti-methicillin-resistant *Staphylococcus aureus* agent levonadifloxacin: Therapeutic role in nosocomial and community infections. Indian J Med Microbiol. 2019;37(4):478-87.
15. Bhagwat SS, Nandanwar M, Kansagara A, Patel A, Takalkar S, Chavan R et al. Levonadifloxacin, a Novel Broad-Spectrum Anti-MRSA Benzoquinolizine Quinolone Agent: Review of Current Evidence. Drug Design, Development Therapy. 2019;13:4351-65.
16. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J et al. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med. 2020;201(11):1380-88.
17. Sharifipour E, Shams S, Esmkhani M, Khodadadi J, Fotouhi-Ardakani R, Koohpaei A, et al. Evaluation of bacterial co-infections of the respiratory tract in COVID-19 patients admitted to ICU. BMC Infect Dis. 2020;20(1):646.
18. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. J Infect. 2020;81(2):266-75.
19. Dhesi Z, Enne VI, Brealey D, Livermpre DM, High J, Russell C et al. Organisms causing secondary pneumonias in COVID-19 patients at 5 UK ICUs as detected with the Film Array test. medRxiv. 2020.
20. Zhu X, Ge Y, Wu T, Zhao K, Chen Y, Wu B et al. Co-infection with respiratory pathogens among COVID-2019 cases. Virus Res. 2020;285:198005.
21. Bakthavatchalam YD, Shankar A, Muniyasamy R, Peter JV, Marcus Z, Triplicane Dwarakanathan H et al. Levonadifloxacin, a recently approved benzoquinolizine fluoroquinolone, exhibits potent *in vitro* activity against contemporary *Staphylococcus aureus* isolates and Bengal Bay clone isolates collected from a large Indian tertiary care hospital. J Antimicrobial Chemotherapy. 2020;75(8):2156-9.
22. Dubois J, Dubois M. Levonadifloxacin (WCK 771) exerts potent intracellular activity against Staphylococcus aureus in THP-1 monocytes at clinically relevant concentrations. J Med Microbiol. 2019;68(12):1716-22.
23. Patel A, Sangle GV, Trivedi J, Shengule SA, Thorve D, Patil M et al. Levonadifloxacin, a Novel Benzoquinolizine Fluoroquinolone, Modulates Lipopolysaccharide-Induced Inflammatory Responses in Human Whole-Blood Assay and Murine Acute Lung Injury Model. Antimicrob Agents Chemother. 2020;64(5):e00084-20.

Cite this article as: Saseedharan S, Aneja P, Chowti A, Debnath K, Mehta KD, Sonone P. Efficacy and safety of intravenous and/or oral levonadifloxacin in the management of secondary bacterial pulmonary infections in COVID-19 patients: findings of a retrospective, real-world, multi-center study. Int J Res Med Sci 2021;9:2933-9.