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MONOGRAPH

ZABOFLOXACIN FOR CHRONIC BRONCHITIS

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SUMMARY

Treatment of lower respiratory tract infection poses as an ongoing challenge among respiratory tract diseases. Bacterial infections are causes of acute exacerbations in chronic bronchitis and indications for antibacterial therapy. Several antibiotics were applied to treat bacterial infections in chronic bronchitis, among them fluoroquinolones are considered potent, broad-spectrum agents with excellent tissue penetration. This monograph focuses on zabofloxacin, a novel fluoroquinolone agent recently approved and launched in South Korea, and summarizes the drug's antibacterial efficacy, pharmacokinetic properties and toxicity. Recent advances concerning fluoroquinolones in chronic bronchitis will be discussed, along with a comparison between zabofloxacin and moxifloxacin. Zabofloxacin has proved to be noninferior to moxifloxacin against major community-acquired Gram-positive and Gram-negative respiratory tract pathogens and found to be well tolerated in both oral and parenteral administrations. These features can make it a potential antimicrobial agent in therapy of chronic bronchitis and other lower respiratory tract infections.

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BACKGROUND

Lower respiratory tract infection (LRTI) comprises bronchitis, bronchiolitis and pneumonia. These clinical pictures are further specified as community-acquired pneumonia, ventilator-associated pneumonia, acute and chronic bronchitis (CB), and bronchiectasis with or without cystic fibrosis (1). CB is a common syndrome in chronic obstructive pulmonary disease (COPD). It has several clinical consequences, including decline in lung function, greater risk of airflow obstruction development in smokers, predisposition to LRTI, intermittent exacerbations and worse overall patient conditions (2).

Acute exacerbations in CB (AECB) are characterized by cough, sputum and dyspnea that are associated with

infections and noninfective agents (e.g., air pollution, allergens, dust and cigarette smoke). With regards to infections, bacterial pathogens are identified most frequently in acute AECB, as they account for 70-80% of all cases (3, 4).

Three major groups of pathogens have been identified as causes of acute exacerbation by infecting the lower respiratory tract, namely respiratory viruses, aerobic Gram-positive bacteria and Gram-negative bacteria (5).

Regarding respiratory virus infections, several studies showed significant incidence of influenza virus in acute exacerbations, but parainfluenza, rhinovirus, coronavirus, adenovirus and respiratory syncytial virus were also frequently identified. Although viral infections account for 20-30% of all cases, they are often complicated by bacterial superinfection (6). Among bacterial infections, pathogens of atypical pneumonia cause 5-10% of all infections in AECB, with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* being the leading pathogens; by contrast *Legionella* spp. appear rarely (6-8). The dominant community-acquired bacteria —namely *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pneumoniae*— account for 60-70% of AECB. LRTIs with *Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus* occur usually in hospitalized patients with impaired lung function (9). The above-mentioned major respiratory bacterial pathogens frequently develop resistance against commonly used antimicrobials such as β-lactams, sulfamethoxazole–trimethoprim, macrolides and fluoroquinolones (10).

Successful treatment of AECB includes antibacterial agents; however, first-line options vary depending on severity of AECB and comorbidities. Antibiotic therapy regimens include β-lactams (amoxicillin, amoxicillin + clavulanate, cephalosporins), macrolides (azithromycin) and fluoroquinolones (levofloxacin, moxifloxacin) (11).

FLUOROQUINOLONES

Fluoroquinolones are synthetic agents and target bacterial DNA synthesis. Their common structure includes a bicyclic ring with a fluorine atom at position C-6. They are broad-spectrum antibacterials and exhibit bactericidal effects against major respiratory tract pathogens (12). Several generations of fluoroquinolones were introduced into clinical practice, as structure modifications enhanced their tissue penetration and extended their antibacterial spectrum. Among them, levofloxacin and moxifloxacin were applied in the treatment of respiratory tract infections (13, 14).

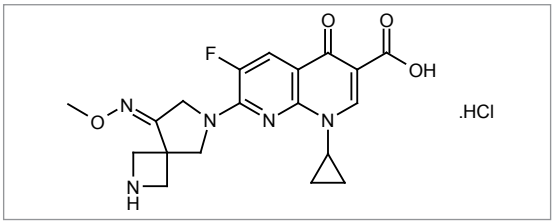

Figure 1. Chemical structure of zabofloxacin

Levofloxacin is the active isomer of ofloxacin and has a bactericidal effect against both Gram-negative and Gram-positive bacteria. Moxifloxacin is characterized by antibacterial effects against major respiratory tract pathogens including Gram-positives and Gram-negatives (15). Fluoroquinolone resistance is widespread among medically important pathogens and it particularly played a role in the selection of methicillin-resistant *S. aureus* clones (16).

In recent years, the identification of new agents has been in focus to obtain antibacterials with potency against pathogens that are already resistant to current fluoroquinolones. This goal was achieved by structure–activity relationship studies to detect substituents that have high affinity for binding to both DNA gyrase and topoisomerase IV enzymes. Among the developed agents, zabofloxacin has undergone clinical testing as it showed increased antibacterial activity including against strains exhibiting resistance to current fluoroquinolones (15, 17).

Zabofloxacin is a fluorinated quinolone with broad-spectrum antibacterial activity manufactured by Dong Wha Pharmaceutical Co., Ltd. (Republic of Korea). There are two formulations of zabofloxacin: zabofloxacin hydrochloride (DW-224a; Fig. 1) and aspartate (DW-224aa) (18, 19). Zabofloxacin was first approved for the treatment of acute bacterial exacerbation of COPD in March 2015 in South Korea where it was subsequently launched in March 2016 (20, 21). Dong Wha has obtained approval from the U.S. Food and Drug Administration to conduct a phase III trial in patients with community-acquired pneumonia (21).

ANTIBACTERIAL ACTIVITY

It has been demonstrated that zabofloxacin achieves bactericidal effect in vitro and in vivo against major Gram-positive and Gram-negative community-acquired respiratory tract pathogens namely, *S. pneumoniae*, *S. aureus, H. influenzae* and *M. catarrhalis.* Antibacterial activity of

zabofloxacin against *K. pneumoniae* was also studied and it was found equally effective as moxifloxacin. In the case of fluoroquinolone-resistant strains of *S. aureus*, zabofloxacin showed enhanced bactericidal activity, as the MIC value was decreased. By contrast, zabofloxacin has no relevant antibacterial efficacy against *P. aeruginosa* and *A. baumannii* (15, 18, 22). The antibacterial efficacy of zabofloxacin against major respiratory tract pathogens is shown in Table I.

In a phase III study, microbiological response was tested during zabofloxacin (367 mg once daily for 5 days) or moxifloxacin (400 mg once daily for 7 days) therapy against major respiratory tract pathogens, namely *H. influenzae, P. aeruginosa, S. pneumoniae* and *M. catarrhalis*. The overall microbiological response was favorable in 62.8% of the zabofloxacin-treated patients and 64.1% of the moxifloxacin group with statistically no significance ($P = 0.90$) between the two treatment regimens (23).

PRECLINICAL PHARMACOLOGY

The pharmacokinetic features of zabofloxacin hydrochloride were studied in beagle dogs. The orally administered zabofloxacin hydrochloride was given at 10, 30 and 90 mg/kg/day for a total of 4 weeks. Fast absorption of the agent was seen, as 30 minutes after the administration, detectable zabofloxacin concentration was in plasma. In 1 hour, the 10 mg/L C_{max} value was reached in plasma (24).

Zabofloxacin pharmacokinetic parameters were set in a rat model as well. Single dose 20 mg/kg zabofloxacin hydrochloride was orally administered to the animals. The C_{max} was 1.8 ± 0.8 mg/L and it was reached within 33.8 ± 18.9 min. The half-life of zabofloxacin was 107 ± 13.3 min (25, 26).

Subacute toxicity was analyzed in beagle dogs. All tested animals presented vomiting and salivation at the 30 and 90 mg/kg/day doses, although only one presented these adverse events at the 10 mg/kg/day dose. Decreased food intake and subsequent body weight loss and anorexia were observed in the 90 mg/kg/day group at day 20 and day 28. Total serum cholesterol increased significantly in the 30 and 90 mg/kg/day group in the fourth week of the study. Electrocardiogram showed a trend toward increased QT intervals at 90 mg/kg/day. Testicle atrophy was detected and consequently, oligo and aspermia were observed. Thymus, spleen and adrenal gland atrophy was found with the 30 and 90 mg/kg/day doses (24).

CLINICAL STUDIES

So far, three clinical studies have been completed regarding zabofloxacin's antibacterial efficacy and pharmacokinetic profile. A phase I clinical trial compared the pharmacokinetic profile of zabofloxacin 183 and 367 mg to that of levofloxacin 250 mg (ClinicalTrials.gov

Table I. *Zabofloxacin and moxifloxacin MIC values for major respiratory tract pathogens.*

Organism	Antibacterial agents	MIC range	MIC_{90}	Ref.
S. pneumoniae	Moxifloxacin	0.125-0.5	0.5	(18)
	Zabofloxacin	0.015-0.06	0.03	
S. aureus, MRSA FQ-resistant	Moxifloxacin	0.03-64	16	(18)
	Zabofloxacin	0.008-32	4	
S. aureus FQ-susceptible	Moxifloxacin	0.015-0.25	0.06	(18)
	Zabofloxacin	0.008-0.06	0.03	
K. pneumoniae	Moxifloxacin	0.03-4	1	(18)
	Zabofloxacin	0.06-8	1	
P. aeruginosa	Moxifloxacin	0.125-64	16	(23)
	Zabofloxacin	0.125-32	8	
A. baumannii	Moxifloxacin	0.015-8	4	(18)
	Zabofloxacin	0.008-8	4	
H. influenzae	Moxifloxacin	0.015-0.06	0.06	(18)
	Zabofloxacin	0.008-0.03	0.03	
M. catarrhalis	Moxifloxacin	0.016-0.063	0.063	(23)
	Zabofloxacin	0.004-0.016	0.016	

All values are in mg/L. MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus;* FQ, fluoroquinolone.

Identifier NCT02212795). Another phase I trial compared the pharmacokinetic features of zabofloxacin hydrochloride (DW-224a) and zabofloxacin aspartate (DW-224aa) (ClinicalTrials.gov Identifier NCT01341249). A phase III clinical study was conducted to compare the efficacy of zabofloxacin 367 mg and moxifloxacin 400 mg treatment regimens (ClinicalTrials.gov Identifier NCT01658020). A phase II clinical study was also organized although it has been terminated (ClinicalTrials.gov Identifier NCT01081964).

The randomized, open-label, single-dose, phase I study comparing zabofloxacin hydrochloride and aspartate enrolled 29 healthy males. The pharmacokinetic features were established after oral administration of 366.7 mg zabofloxacin hydrochloride and 366.5 mg zabofloxacin aspartate. The peak serum concentration (C_{max}) values were 1.9 ± 0.5 mg/L and 2 ± 0.3 mg/L and these concentrations were reached in plasma between 0.5-4 h and 0.8-3 h, respectively. The half-life of zabofloxacin was 8 ± 1 h for both formulations (19).

The single oral doses of 366.7 mg zabofloxacin hydrochloride and 366.5 mg zabofloxacin aspartate were found to be well tolerated among healthy male volunteers. The most frequent adverse events were nausea (7% of the subjects), hypotension (3%), somnolence (3%) and increase of blood phosphokinase (3%). By contrast, a typical adverse event of fluoroquinolones — the prolongation of QT interval— was not detected (19).

The pharmacokinetic properties of zabofloxacin and other respiratory fluoroquinolones are listed in Table II.

The multicenter, double-blind, randomized, phase III noninferiority clinical trial compared the efficacy of oral zabofloxacin (367 mg once daily for 5 days) with that of moxifloxacin (400 mg once daily for 7 days) (23). Altogether 345 COPD patients with moderate exacerbations during chronic bronchitis and similar clinical baseline characteristics were enrolled. The overall clinical cure rate for zabofloxacin was 88.2% and that for moxifloxacin was 89.1% with statistically not significant differences ($P = 0.89$). This result confirmed that zabofloxacin achieved the same clinical outcome as moxifloxacin at the end of the tested period.

Zabofloxacin and moxifloxacin were compared in a subgroup of patients without chronic bronchitis, but suffering from LRTI, and 85.9% and 84.2% cure rates were observed, respectively, with no statistically significant differences ($P = 0.76$) (23).

Adverse events during zabofloxacin (367 mg once daily for 5 days) and moxifloxacin (400 mg once daily for 7 days) therapy were analyzed in the phase III noninferiority clinical trial. Among all tested patients, 36.6% of patients on zabofloxacin and 38.9% of patients treated with moxifloxacin developed adverse reactions, and no statistical difference was detected ($P = 0.65$) between the two treatment regimens (23).

Various mild adverse events occurred during zabofloxacin therapy. Among them, gastrointestinal disorders, namely nausea, diarrhea, dyspepsia, vomiting and abdominal discomfort, appeared in 0.6-2.3% of all COPD patients enrolled in the study. Other side effects such as headache, dizziness, paresthesia, pruritus, rash, erythema, chest discomfort, palpitations and flank pain developed only in 0.6-1.7% of individuals included in the study (23).

CONCLUSIONS

LRTI is still a great challenge to treat, as infectious agents influence the overall condition of the patient. Antimicrobial agents are required for therapy success and several classes of antibiotics have been employed in treatment regimens. However, nowadays, pathogens are increasingly developing resistance to classic antibiotics. Therefore, novel antimicrobial agents are needed to meet this challenge.

Table II. *Pharmacokinetic features of zabofloxacin and respiratory fluoroquinolones.*

Fluoroquinolone agent	Protein binding (%)	Urinary fraction (%)[a]	Bioavailability (%)	C_{max} (mg/L)	AUC (mg·h/L)	$t_{1/2}$ (h)	Ref.
Levofloxacin	24-38	87	99	6.2	47	6-7	(13)
Moxifloxacin	50	20	90	4.5	48	12	(13)
Zabofloxacin	NA	NA	NA	2	11	8	(19)

[a]Urifnary fraction excreted unbound.

Zabofloxacin, a novel fluoroquinolone agent detailed in this monograph, offers an enhanced antibacterial effect against major respiratory tract pathogens (MIC_{90} = 0.016-0.03 mg/L) compared to earlier classes of fluoroquinolones. However, further pharmacokinetic/pharmacodynamic studies are required to set clinical breakpoints and to ensure these MIC_{90} values of zabofloxacin have in vivo bactericide effects and result in therapy success.

The improved safety profile and decreased toxicity based on phase I and III clinical trials indicate the agent has potential in clinical practice. Zabofloxacin was found to be well tolerated during clinical trials as only minor adverse events (mainly gastrointestinal disorders) occurred and these appeared in low prevalence (0.6-7% of tested subjects) (19, 23).

Oral zabofloxacin (367 mg once daily for 5 days) was noninferior to oral moxifloxacin (400 mg once daily for 7 days) for treatment of patients with COPD exacerbations (23). On the basis of this treatment protocol, zabofloxacin can be a potential treatment option for COPD patients with moderate exacerbations in an outpatient setting and in community-acquired acute respiratory tract infections. By contrast, zabofloxacin showed no potency against pathogens involved in ventilator-associated pneumonia and bronchiectasis in cystic fibrosis patients, with MIC_{90} values of 8 and 4 mg/L, respectively, against *P. aeruginosa* and *A. baumannii*.

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