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Delafloxacin: A Novel Fluoroquinolone Introduced in Clinical Trials

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Abstract

Delafloxacin is a new broad-spectrum fluoroquinolone agent. It has the common bicyclic quinolone ring with additional substitutions namely, a chlorine in position C8 and a heteroaromatic ring in position N1. Mechanism of action of delafloxacin is the inhibition of bacterial DNA synthesis, it targets both bacterial gyrase and topoisomarase IV enzymes. During *in vitro* and *in vivo* investigations delafloxacin exhibited bactericid effect against several major pathogens, including *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and *Neisseria gonorrhoeae*. Clinical trials have showed that delafloxacin is effective in skin and soft tissue infection caused by *S. aureus*, even against ciprofloxacin resistant pathogens. Delafloxacin was well-tolerated during both per os and parenteral administrations. Based on its pharmacokinetic and pharmacodynamic features delafloxacin can be a potential antimicrobial agent in therapy of acute bacterial skin and soft tissue infections and in community-acquired pneumonia in the future.

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Quinolones were developed and introduced into clinical practice in the 1960s. During the past decades numerous agents have been synthetised by addition of certain substituents on the basic quinolone ring namely, in position C1 cyclopropyl or difluorophenyl, in position C6 a fluorine and in position C8 a halogen, metoxy or fused third ring. These structure modifications resulted in development of ofloxacin, ciprofloxacin, norfloxacin, levofloxacin, moxifloxacin and several other agents [1-4]. All above mentioned structure modifications yielded fluoroquinolones and resulted in improved antibacterial efficacy, broaden spectrum and enhanced tissue penetration [5].

Delafloxacin (WQ-3034) is a novel fluoroquinolone agent, discovered by Wakunaga Pharmaceutical Co., Ltd., Osaka & Hiroshima, Japan. Its chemical structure is 1-(6-amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-hydroxyazetidin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid. This structure has three unique features: lack of a strongly basic group in position C7 that confers weak acidity; a chlorine in position C8 that exhibits a strong electron withdraw on aromatic ring; heteroaromatic substitution in position N1 that leads to a larger molecular surface compared to currently used fluoroquinolones [6]. The anionic structure of delafloxacin increases its potency in acidic environment, therefore its antibacterial activity is enhanced in site of infection with reduced pH (e.g.: skin and soft tissue infections). This feature makes delafloxacin special among fluoroquinolones as ciprofloxacin and moxifloxacin lose potency in acidic environment [7,8]. Delafloxacin is a broad-spectrum agent, as it targets both DNA gyrase and topoisomerase IV enzymes [9]. Based on in vitro testing delafloxacin proved to be effective with MICs between 0.004-0.015 mg/L against various pathogens namely, *Streptococcus pneumoniae*, *Staphylococcus aureus, Haemophilus influenzae*, *Moraxella catarrhalis*. Delafloxacin MIC values ranged between 0.12 and 0.5 mg/L against levofloxacin resistant (MIC >4 mg/L) *S. pneumoniae* strains [10]. Delafloxacin MICs were between 0.008 and 1 mg/L in ciprofloxacin resistant (MIC 0.5-256 mg/L) *S. aureus* strains [6]. In the case of *Neisseria gonorrhoeae* delafloxacin exhibited bactericid effect with MICs between 0.001 and 0.25 mg/L that is comparable to those of ceftriaxone (0.001 to 0.25 mg/L) and cefixime (0.001 to 0.5mg/L)[11]. Appart from bactericid effect delafloxacin inhibits biofilm formation of *S. aureus* [12]. Several murine lung infectious models showed in vivo efficacy of delafoxacin in infections caused by *S. aureus, S. pneumoniae* and *Klebsiella pneumoniae* [13, 14].

Delafloxacin has been introduced into clinical trials to evaluate its pharmacokinetic properties and to compare its antibacterial efficacy with other antimicrobials. A Phase 1 clinical trial investigated a single per os dose of 900 mg delafloxacin in 30 healthy individuals under different feeding conditions namely, individuals under fasting conditions for at least 10 hours; subjects under fed conditions of standardized FDA high fat breakfast 30 min before dosing; individuals in fasting followed by a high fat meal 2 hours after dosing. The pharmacokinetic parameters of delafloxacin did not differ in each group as peak serum concentration (C_{max}) was 11.5, 9.14 and 11.8 mg/L, respectively. The time to reach C_{max} was 1.25, 2.5 and 1.5 hours while half-life time of delafloxacin was 14.1, 12.9 and 12 hours, respectively. During this study delafloxacin was well-tolerated but the following mild adverse events appeard in all three groups: diarrhoea, nausea, presyncope, headache, vaginal disorders or pharyngitis [15].

A randomized, double-blind, placebo-controlled, 4-period crossover study was conducted in 52 healthy volunteers to evalute effect on QTcF intervals of intravenous 300 and 900 mg doses of delafloxacin. None of the doses resulted in a clinically relevant increase in QTcF iterval [16].

A Phase 2 study compared antibacterial efficacy of delafloxacin to tigecyclin in skin and soft tissue infections of 150 patients. Doses of 300 and 450 mg delafloxacin were administered parenterally every 12 hours and compared to tigecycline iv dose of 100 mg plus 50 mg every 12 hours. The study was performed for 5-14 days based on clinical outcome. No significant differences were found between the three treatment options as each was effective in skin and soft tissue infecions caused by *S. aureus* and methicillin-resistant *S. aureus*.The ciprofloxacin MIC values of pathogens in this study ranged between 0.12 and 32 mg/L, by contrast delafloxacin MIC values varied between 0.004 and 0.12 mg/L. Delafloxacin was well-tolerated during

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this multicenter study only mild side effects as nausea, diarrhoea, headache, insomnia and fatigue appeared during the intravenous adminsitration [8].

A Phase 2 clinical trial investigated clinical cure rate of skin and skin structure infections after treatment with different antimicrobials namely, 300 mg delafloxacin, 600 mg linezolid and 15 mg/kg vancomycin. Each agent was administered parenterally and endpoint was the complete resolution of baseline symptoms. Cure rate was significantly higher with delafloxacin compared to vancomycin. These differences were significant in obese patients, but not in non-obese individuals. In the case of delafloxacin versus linezolid, no significant differences were detected [17].

Two Phase 3 trials are ongoing or has been completed with delafloxacin and both investigate therapy of acute bacterial skin and skin structure infections. In the first study delafloxacin (300 mg intravenously) b.i.d. for up 5–14 days while the second one compares delafloxacin 300 mg intravenously b.i.d. for 3 days followed by 450 mg oral b.i.d. for up 5–14 days total to vancomycin (15 mg/kg intravenously) + aztreonam (2 g intravenously) [18]. Based on currently available data delafloxacin is a promissing fluoroquinolone agent. It is highly active against major Gram-positive and Gram-negative respiratory tract pathogens including *S. aureus, S. pneumoniae, H. influenazae* and *M. catarrhalis*. It showes bactericid effect in low-concentration (0.008-1 mg/L) even against strains resistant to ciprofloxacin and levofloxacin. Delafloxacin can be a potential antimicrobial agent in therapy of skin and soft tissue infections and community-acquired pneumonia in the future.

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Competing Interests

The authors declare that there is no competing interest.

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