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REVIEW

Emerging treatment options for acute bacterial skin and skin structure infections: focus on intravenous delafloxacin

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Abstract: The increase in hospitalization due to acute bacterial skin and skin structure infections (ABSSSI) caused by resistant pathogens supports the need for new treatment options. Antimicrobial options for ABSSSI that provide broad-spectrum coverage, including gram-negative pathogens and multidrug-resistant gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are limited. Delafloxacin is a novel fluoroquinolone available as intravenous and oral formulations and is characterized by an increased efficacy in acidic environments and activity on bacterial biofilm. Delafloxacin displays enhanced in vitro activity against MRSA, and enterococci, while maintaining efficacy against gram-negative pathogens and anaerobes. Delafloxacin has been studied for the treatment of ABSSSI and respiratory infections. Phase III studies have demonstrated noninferiority of delafloxacin compared to vancomycin, linezolid, tigecycline, and the combination of vancomycin plus aztreonam in the treatment of ABSSSI. Due to its favorable pharmacokinetic characteristics, the wide spectrum of action, and the potential for sequential therapy, delafloxacin represents a promising option in the empirical and targeted treatment of ABSSSI, both in hospital- and in community-based care.

Keywords: bacterial skin and skin structure infections, multidrug-resistant bacteria, methicillin-resistant *Staphylococcus aureus*, delafloxacin

Current scenario of complicated skin and soft tissue infections

The clinical spectrum of skin infections is highly variable and ranges from mild forms to life-threatening diseases.[1] Among these, acute bacterial skin and skin structure infections (ABSSSI), formerly referred to as complicated skin and soft tissue infections, represent a frequent reason for hospital admission and a common cause of morbidity in the community.[2,3] A nearly 3-fold increase in ABSSSI visit rates had been documented among patients presenting to the emergency departments with skin abscesses and cellulitis in the USA.[2,4]

Staphylococcus aureus represents the most common cause of ABSSSI, and methicillin-resistant *S. aureus* (MRSA) is often the most frequently isolated pathogen in complicated forms.[3,5] In Europe, despite a high variability in prevalence, MRSA isolation can reach up to 25% in ABSSSI, especially in those areas where antimicrobial resistance represents a concern (e.g., Italy, Greece, and Eastern Europe).[6,7] In the USA, community-acquired (CA) MRSA strains are endemic and frequently associated with skin infections and purulent skin abscesses, with reported outbreaks in military

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recruits, athletes, and prisoners.[8,9] MRSA prevalence among patients with ABSSSI undergoing microbiological cultures was reported as high as 75%–80% in the USA.[3,10,11]

The increase in hospital admissions required to treat ABSSSI with intravenous (IV) antibiotics along with the spread of multidrug-resistant (MDR) bacteria have caused a considerable impact on hospital stay and patient's morbidity, reinforcing the need for new treatment options.[12]

New therapeutic options for the treatment of ABSSSI have recently become available and offer advantages such as MRSA coverage as well as the possibility for outpatient treatment (e.g., IV to oral switch and/or infrequent administration).[13]

New therapeutic options for complicated skin and soft tissue infections

Antimicrobials that are commonly used in the treatment of ABSSSI due to methicillin-susceptible *S. aureus* (MSSA) include beta-lactams, especially oxacillin and flucloxacillin, fluoroquinolones (e.g., moxifloxacin and levofloxacin), and clindamycin.[1] MRSA is suspected in the presence of several risk factors, including nosocomial or health care-associated infection, previous MRSA infection or colonization, recent exposure to antimicrobial agents, and abscesses.[14,15]

Vancomycin has been considered for decades as the drug of choice for ABSSSI caused by MRSA. In two European surveys documenting the choices of antibiotics for the treatment of ABSSSI, vancomycin was found to be the most used antimicrobial in both 2010 and 2015.[16,17] Various studies, however, have now highlighted that vancomycin presents several limitations in the treatment of MRSA. First, a progressive increase in vancomycin minimum inhibitory concentrations (MICs) over the years was observed in *S. aureus* and was associated with less favorable clinical outcomes compared to isolates with MIC below 1 mg/L.[18] Second, a decreased efficacy of vancomycin has been documented in severe infections caused by MSSA compared to MRSA.[19,20] Third, in order to achieve adequate plasmatic concentrations, therapeutic drug monitoring is needed to minimize the risk of nephrotoxicity.[21] Finally, vancomycin requires twice-daily IV administration, limiting the possibility for outpatient parenteral antibiotic therapy.

Several novel therapeutic options have become available for the treatment of ABSSSI caused by MDR bacteria, including strains with increased vancomycin MICs (Table 1).[13]

Data on the efficacy of new agents for ABSSSI are mainly derived from noninferiority trials and do not directly compare the efficacy of newer compounds. Nevertheless, several characteristics of newly studied molecules appear promising for ABSSSI treatment, including wide spectrum of action, favorable pharmacokinetics (PK) and pharmacodynamics, and high tolerability.[13]

Characteristics and limitations of the molecules that are currently available and under investigation for the treatment of ABSSSI are reported in Table 1.

Table 1 Characteristics of antimicrobials that are available or in late stage of development for the treatment of ABSSSI

	Bactericidal activity	Prolonged half-life	MRSA activity	Equal activity on MRSA and MSSA	Oral and IV formulation	Gram-negative activity
Ideal drug	Yes	Yes	Yes	Yes	Yes	Yes
Available for use						
Oxacillin	Yes	No	No	No	Yes	Limited
Moxifloxacin	Yes	Yes (OD)	No	No	Yes	Moderate
Levofloxacin	Yes	No	No	No	Yes	Moderate
Trimethoprim/ sulfamethoxazole	Yes	No	Yes/No	No	Yes	Limited
Clindamycin	Yes	No	Yes/No	No	Yes	Limited
Daptomycin	Yes	Yes (OD)	Yes	Yes	No	No
Tigecycline	No	No	Yes	Yes	No	Yes
Vancomycin	Yes	No	Yes	No	No	No
Linezolid	No	No	Yes	Yes	Yes	No
Ceftaroline	Yes	No	Yes	Yes	No	Moderate
Dalbavancin	Yes	Yes (OW)	Yes	Yes	No	No
Oritavancin	Yes	Yes (OW)	Yes	Yes	No	No
Tedizolid	No	Yes (OD)	Yes	Yes	Yes	No
Phase III trials completed						
Telavancin	Yes	Yes (OD)	Yes	Yes	No	No
Delafloxacin	Yes	No	Yes	Yes	Yes	Yes

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; OD, once daily; OW, once weekly.

Delafloxacin

Newer quinolones and delafloxacin

Delafloxacin belongs to the quinolone class of antibiotics, synthetic antimicrobials developed in the 1960s. The quinolones exert their activity by generating a complex between a DNA molecule and two enzymes (e.g., DNA gyrase and topoisomerase IV), thus inhibiting bacterial DNA supercoiling and synthesis.[22,23] Since the discovery of nalidixic acid, the first quinolone agent produced, several new agents have been manufactured by alteration of the bicyclic quinolone ring. Specifically, the addition of fluorine to the chemical structure led to the generation of the widely used fluoroquinolones (e.g., ciprofloxacin, levofloxacin, moxifloxacin, and so on), characterized by a wider antibacterial spectrum compared to the first generation of quinolones.[24] Resistance to ciprofloxacin and levofloxacin, however, has developed starting from the 1990s, especially among gram-negative bacteria, thus becoming a prevalent clinical issue that is threatening the efficacy of these drugs.[25] Studies analyzing the relationship between quinolone structure and activity have led to the development of new agents targeting both gyrase and topoisomerase IV, broadening the spectrum of activity against gram-positive and gram-negative bacteria and overcoming antimicrobial resistance.[26] Five new quinolones are currently undergoing clinical testing, including delafloxacin (WQ-3034), avarofloxacin (JNJ-Q2), zabofloxacin (DW224a), finafloxacin (BAY35-3377), and non-fluorinated nemonoxacin (TG-873870).[23]

Here, we review the characteristics and potential use of delafloxacin in clinical practice.

Chemical structure and properties

Delafloxacin has a molecular weight of 440.763 g/mol and presents a larger molecular surface compared to other quinolones due to a heteroaromatic substitution at N-1. Delafloxacin presents a weak acid character caused by the absence of the strongly basic C-7 group that is typical of the quinolone structure. Furthermore, this molecule is characterized by a strong electron-withdrawing effect on the aromatic ring due to the presence of a chlorine atom at C-8 position.[27] Chemical structure of delafloxacin is presented in Figure 1.

At neutral pH, delafloxacin exists in a deprotonated form, and its anionic structure appears to enhance its potency in an acidic environment.[28] Due to these characteristics, delafloxacin activity in low pH environment including phagolysosomes, inflammatory cells, and infected tissues appears unique compared to older molecules.[27,28] Furthermore, the risk for resistant strain selection is reduced and the activity toward fluoroquinolones nonsusceptible strains is enhanced by delafloxacin's dual mechanism of action toward both DNA gyrase and topoisomerase IV.[29]

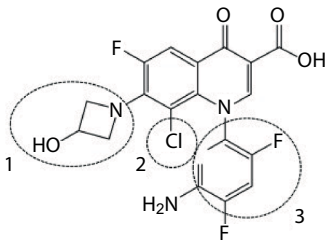

Figure 1 Chemical structure of delafloxacin.
Notes: Three characteristics differentiate delafloxacin from other quinolones: 1) the lack of a protonable substituent group in position 7 that confers a weak acid character to the molecule; 2) the presence of a chlorine atom in position 8 that reduces the reactivity of the heterocycle, stabilizing the molecule; and 3) the aromatic ring attached to N1 that increases the surface of the molecule.

Delafloxacin spectrum of activity

Delafloxacin displays a broad spectrum of activity against a variety of gram-positive pathogens, while maintaining activity against gram-negative bacteria and anaerobes.[30] Compared to other quinolones such as levofloxacin and ciprofloxacin, delafloxacin has displayed greater in vitro activity against both quinolone-susceptible and quinolone-resistant gram-positive pathogens, including MSSA, MRSA, *Streptococcus pyogenes*, and enterococci.[31] Against quinolone-susceptible *Streptococcus pneumoniae*, delafloxacin showed MIC_{90} of 0.015 μg/mL and was 32-, 64-, and 128-fold more effective than moxifloxacin, levofloxacin, and ciprofloxacin, respectively. Against quinolone-resistant strains of *S. pneumoniae*, the MIC_{90} of delafloxacin was 0.12 μg/mL compared to MIC_{90} of 8, 16, and 64 μg/mL for trovafloxacin, levofloxacin, and ciprofloxacin, respectively.[31]

Delafloxacin has an excellent in vitro activity against staphylococci, showing MIC_{90} ranging from 0.12 to 0.5 μg/mL for MRSA and 0.25 μg/mL for coagulase-negative staphylococci.[27,31] Compared with moxifloxacin, delafloxacin showed superiority toward both levofloxacin-susceptible and levofloxacin-resistant MRSA strains. The in vitro activity of delafloxacin compared to levofloxacin and ciprofloxacin was recently reported from two global Phase III studies investigating 685 *S. aureus* isolates. According to Clinical and Laboratory Standards Institute breakpoints. 34% of *S. aureus* isolates were levofloxacin resistant. The delafloxacin MIC_{90} value against levofloxacin-nonsusceptible *S. aureus*, MRSA, and MSSA isolates was 0.25 μg/mL.[32]

Delafloxacin was more active than other quinolones against quinolone-susceptible enterococci, showing MIC_{90} for *Enterococcus faecalis* of 0.03 μg/mL and an MIC_{50} for *Enterococcus faecium* of 0.25 μg/mL.[31]

Against quinolone-susceptible Enterobacteriaceae, delafloxacin showed comparable activity to levofloxacin and ciprofloxacin, while increased activity was shown against quinolone-resistant strains of *Haemophilus influenzae*, *Moraxella catarrhalis*, *Legionella* spp., *Pseudomonas aeruginosa*, and *Helicobacter pylori*.[33]

Delafloxacin is active against microorganisms responsible for sexually transmitted diseases, such as *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*. Low MICs have also been shown against *Neisseria gonorrhoeae*, including ciprofloxacin-resistant strains.[34,35]

Delafloxacin activity in acidic environments and on biofilm

In acidic environments, the activity of delafloxacin appears enhanced.[36] In a study including 35 strains of *S. aureus* with clinically relevant resistance mechanisms, delafloxacin showed significantly lower MICs (3–5 $\log_2$ dilutions) compared to moxifloxacin. Delafloxacin's superiority was further enhanced at lower pH (pH 5.5) with the MIC decreasing by 5 $\log_2$ dilutions. Compared to moxifloxacin, whose activity is reduced by the acidic pH present in vacuolar subcellular compartments, accumulation of delafloxacin increased 10-fold in bacteria and at an intracellular level. These data support the use of delafloxacin for the treatment of staphylococcal infections in acidic environments such as biofilm-associated infections and abscesses. In these environments, antibiotics have usually reduced activity. Delafloxacin use could be promising in other environments characterized by acidic pH, such as skin and urinary infections.[36]

Against the strains of Enterobacteriaceae collected from patients with urinary tract infection with pH of 6.5 or less, MICs of delafloxacin were 2- to 5-fold lower than those of ciprofloxacin.[37]

Besides its direct antibacterial effect, the inhibition of *S. aureus* biofilm production has also been documented.[38] Due to the acidic environment within biofilms, delafloxacin activity can be enhanced, such that it shows superiority compared to other compounds and similar activity of that of daptomycin. Delafloxacin was able to reduce bacterial viability of over 50% against both MSSA and MRSA, was able to decrease biofilm depth, and appeared more potent compared to daptomycin against MRSA strains.[38]

Delafloxacin PK

Hoover et al summarized the pharmacokinetic properties, safety, and tolerability of single and multiple doses of IV delafloxacin through three Phase I clinical trials, including two randomized, double-blind, placebo-controlled studies and one open-label, randomized, crossover study.[39] In the first study, single ascending doses of IV delafloxacin (from 300 to 1200 mg) were administered to 62 healthy volunteers (52 active, 10 placebo). In the second study, IV delafloxacin was given to 12 healthy volunteers (8 active, 4 placebo) as a single dose of 300 mg on day 1, followed by twice-daily dosing on day 2 through day 14. In the third two-period, two-sequence study, 56 healthy volunteers were randomly assigned to one of two sequences of a single oral dose of delafloxacin (450 mg tablet) or IV delafloxacin (300 mg) in order to determine the absolute bioavailability of the oral formulation of delafloxacin.

Overall, the three studies encompassed 94 healthy volunteers and showed that delafloxacin's half-life ranged from 8.2 to 17.7 hours (with a mean half-life of 12 hours) and had a dose-independent volume of distribution (V_d) of ~35 L (range, 30.2–38.5 L). Delafloxacin C_{max} and area under the concentration–time curve (AUC) values increased proportionally and more than proportionally with increasing doses, respectively.[39]

Accumulation of delafloxacin appeared minimal after multiple doses, showing an accumulation ratio of 1.09 after 14 days of twice-daily IV administration of 300 mg. Mean delafloxacin renal clearance was comparable on day 1 (14.1 L/hour) and day 14 (13.8 L/hour).[39]

Delafloxacin undergoes minimal oxidative metabolism and has a renal excretion predominantly (65%). A mass balance study using radiolabeled delafloxacin in healthy male volunteers studied the excretion of delafloxacin after a single 300 mg IV dose.[40] Overall, 66% of the dose was recovered in the urine, mainly as unchanged delafloxacin. Approximately 29% was recovered in the feces due to biliary excretion and/or transintestinal elimination.

Delafloxacin plasma protein binding (mainly albumin) was ~84% and was not significantly affected by renal impairment.[41] A double-blind, placebo-controlled, Phase I clinical trial investigated the effect of sex and age on delafloxacin PK. The results showed that delafloxacin PK was comparable in men and women, while significantly higher C_{max} and $AUC_{0-\infty}$ were observed in elderly compared to younger patients, probably due to different creatinine clearance values among groups.[42]

Renal impairment appeared to significantly affect delafloxacin clearance. A dosage reduction to 200 mg IV every 12 hours is recommended in the presence of severe renal impairment (creatinine clearance <30 mL/min).[43]

A Phase I, open-label study investigated the PK and safety of a single IV dose of 300 mg delafloxacin in 18 subjects with

mild, moderate, and severe hepatic impairment (Child–Pugh class A, B, and C, respectively) compared with 18 healthy controls.[44] Mean delafloxacin $AUC_{0-\infty}$, C_{max}, exposure, and clearance among patients with liver impairment did not significantly differ from the healthy subjects. Based on these data, dose adjustment of delafloxacin in patients with hepatic impairment is not needed.

Delafloxacin drug–drug interactions

In vitro studies confirmed that delafloxacin does not exert inhibitory effects on hepatic enzymes, except for a mild induction of CYP3A4 enzymes. A Phase I study encompassing 22 healthy subjects investigated the clinical relevance of delafloxacin drug interactions on CYP3A4. Two doses of midazolam were administered in the absence and after 6 days of delafloxacin treatment (450 mg every 12 hours). The 24-hour AUCs of midazolam and its metabolite did not differ before and after delafloxacin administration, suggesting that delafloxacin does not have clinically relevant effects on cytochrome P450 3A4.[45]

Clinical efficacy

Animal models

Studies on animal models identified the AUC/MIC ratio as the most reliable parameter to predict delafloxacin efficacy.[46,47] A murine model of lung infection including MRSA, penicillin-resistant *S. pneumoniae*, and ESBL-producing *Klebsiella pneumoniae* investigated the efficacy of delafloxacin administered IV (300 mg) or orally (450 mg) twice daily. The results confirmed the efficacy of delafloxacin on resistant strains.[46]

Clinical studies

Delafloxacin has been approved by the US Food and Drug Administration for the treatment of ABSSSI in June 2017. Two Phase II and two Phase III trials have analyzed the efficacy of delafloxacin vs comparators in these infections (Table 2).

A Phase II, double-blind clinical trial compared two doses of delafloxacin (300 and 450 mg IV every 12 hours) with tigecycline (100 mg IV followed by 50 mg every 12 hours) administered for 5–14 days in 150 patients with ABSSSI including cellulitis, abscesses, and wound infections.[48] *S. aureus* was isolated in 86.5% of cases, of which ~70% were MRSA and 63% were levofloxacin-resistant strains. Cure rates were 94.3%, 92.5%, and 91.2% among patients treated with delafloxacin 300 mg every 12 hours, delafloxacin 450 mg every 12 hours, and tigecycline 50 mg every 12 hours, respectively.[48]

Another Phase II trial was conducted in a population of 256 adult patients with ABSSSI including cellulitis (45%), abscesses (28.5%), wound infections (25%), and burns (1.5%) to evaluate the efficacy of IV delafloxacin compared to linezolid and vancomycin.[49] Delafloxacin cure rate was 70.4% and was comparable to linezolid (64.9%) and significantly higher than vancomycin (54.1%, p=0.03). Clinical cure rates were similar in the group of patients with MRSA infections, while higher cure rates were achieved by delafloxacin among patients with body mass index ≥30 kg/m^2.[49]

Two Phase III studies, defined as PROCEED, encompassing 660 and 860 patients with ABSSSI and comparing delafloxacin with vancomycin plus aztreonam have been recently concluded.[50,51] The studies analyzed the efficacy and microbiological response of delafloxacin among subjects with various infections including resistant *S. aureus* and gram-negative pathogens. Patients received delafloxacin 300 mg IV every 12 hours or delafloxacin 300 mg IV every 12 hours for 3 days with a mandatory blinded switch to oral delafloxacin 450 mg every 12 hours or vancomycin 15 mg/kg IV with aztreonam between 5 and 14 days. In both studies, the primary European Medicines Agency (EMA) endpoint was the reduction of lesion size in the first 48–72 hours and the clinical response

Table 2 Phase II and III clinical trials analyzing the efficacy of IV delafloxacin in ABSSSI

Study type	Patients (n)	Delafloxacin arm	Comparator(s)	Outcome	Reference
Phase II	150	Two IV doses (300 and 450 mg q12h)	Tigecycline (100 mg first dose, then 50 mg q12h)	Cure rates: 94.3% delafloxacin 300 mg, 92.5% 450 mg, 91.2% tigecycline	48
Phase II	256	300 mg q12h	Linezolid (600 mg IV q12h); vancomycin (15 mg/kg q12h)	Cure rates: 70.4% delafloxacin, 64.9% linezolid, 54.1% vancomycin	49
Phase III	660	300 mg q12h	Vancomycin (15 mg/kg q12h) ± aztreonam	Objective response: 78.2% delafloxacin, 80.9% vancomycin/aztreonam Investigator-assessed cure: 52.0% delafloxacin, 50.5% vancomycin/aztreonam Late follow-up: 70.4% delafloxacin, 66.6% vancomycin/aztreonam	57

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; IV, intravenous; q12h, every 12 hours.

at 28 days. Evaluation of outcomes occurred at 14 and 21–28 days (late follow-up). Compared to the combination of vancomycin plus aztreonam, delafloxacin demonstrated noninferiority in reducing lesion size at the primary infection site at 48–72 hours. Delafloxacin showed noninferiority on assessment of signs and symptoms of infection at the follow-up visit. The outcome of delafloxacin treatment in patients with ABSSSI due to gram-negative pathogens (97 patients, 19%) has been recently reported. [52] *K. pneumoniae* was the most frequent gram-negative isolate (MIC_{50}, MIC_{90}, and MIC ranges were 0.12, 0.25, and 0.03–4 μg/mL, respectively). Clinical response rates among patients treated with delafloxacin compared to vancomycin/aztreonam at 48–72 hours, day 14, and day 21–28 were 85.6% vs 88.3%, 98.7% vs 97.6%, and 97.3% vs 97.4%, respectively. Among gram-positive infections (n=987), objective response rates at 48–72 hours, day 14, and day 21–28 were 87.9% vs 87%, 97.9% vs 98.1%, and 97.2% vs 97.5% in the delafloxacin and comparator arms, respectively.[53] Microbiological eradication rates for infections due to MRSA were 98.1% and 98.0% for patients treated with delafloxacin and vancomycin, respectively.

Delafloxacin is also under investigation for respiratory infections. A Phase II trial in acute exacerbation of COPD demonstrated comparable efficacy to levofloxacin. Delafloxacin is currently being studied in CA pneumonia in comparison to moxifloxacin.[54,55]

Delafloxacin safety

Phase I studies have shown that the occurrence of adverse effects (AEs) is associated with delafloxacin dose. In the dose escalation study, IV delafloxacin doses of 800 mg or more were associated with adverse reactions in over 50% of the participants.[42] AEs were mainly gastrointestinal (e.g., diarrhea). Oral administration of delafloxacin, however, was well tolerated across the dose range (from 50 to 1600 mg).

In the Phase II trial comparing two doses of delafloxacin and tigecycline in ABSSSI, the administration of IV delafloxacin 300 mg every 12 hours was not associated with significant drug toxicity.[48] AEs, mainly nausea and IV infusion-related effects, were more frequent among patients receiving tigecycline and high delafloxacin dose (450 mg every 12 hours). In this study, delafloxacin appeared to be associated with a decrease in glucose plasma levels, although this AE has not been confirmed by other trials.

In the comparative study of delafloxacin, linezolid, and vancomycin in treating ABSSSI, the highest number of AEs was reported in the delafloxacin arm (74.4% compared to 72% for linezolid and 64.6% for vancomycin).[49] Nausea was the most frequent AE. Two cases of elevation of the alanine transaminase and aspartate transaminase levels were reported (one in the delafloxacin and the other in the vancomycin group).

Delafloxacin showed a similar tolerability profile to vancomycin/aztreonam in patients with ABSSSI according to the two recent registrational Phase III trials.[56,57] Rates of treatment-emergent AEs were similar in patients receiving delafloxacin to those receiving vancomycin/aztreonam (47.7% vs 45.1%, respectively). Gastrointestinal-related events including nausea (4.3% vs 6.1%, respectively) and diarrhea (2.0% vs 6.1%, respectively) were the most common treatment-emergent AEs reported. Discontinuation of treatment was reported in 2.4% of patients receiving vancomycin/aztreonam and in 0.8% of patients receiving delafloxacin. Serious AEs were similar in the delafloxacin and vancomycin/aztreonam groups (3.6% vs 3.5%, respectively). No treatment-related deaths were reported in the studies.[56]

To date, no safety study has reported cases of *Clostridium difficile* diarrhea associated with delafloxacin use. This could be related to delafloxacin activity against anaerobes, showing MICs below 0.015 g/mL against *C. difficile*.[31]

No AEs at the level of central nervous system, tendons muscles, joints, and nerves have been reported. No clinically relevant phototoxicity has been demonstrated for delafloxacin.[58]

A randomized, double-blind, placebo-controlled, four-period, crossover study in 52 healthy adults assessed the effect of delafloxacin administered at 300 and 900 mg IV compared to moxifloxacin on the corrected QT interval. No positive relationship between delafloxacin plasma concentrations and corrected QT was demonstrated.[59]

Delafloxacin use in clinical practice

Similar to other fluoroquinolones, delafloxacin presents favorable PK/pharmacodynamics characteristics (e.g., high volume of distribution, good bioavailability) along with a bactericidal activity against both gram-positive and gram-negative pathogens, representing an attractive option for use in clinical practice.

Unique characteristics of delafloxacin include an extended spectrum of activity against MRSA and anaerobes, the enhanced activity in acidic environments, and a favorable tolerability profile demonstrated in clinical trials (Table 3).

Delafloxacin in ABSSSI

Delafloxacin represents a promising option in the empirical and targeted treatment of ABSSSI, including cellulitis, skin

Table 3 Delafloxacin unique characteristics compared to older quinolones

Characteristic	Potential effect in clinical practice
Weak acid character	Enhanced activity in low pH environments including inflammatory cells and infected tissues such as biofilm-associated infections, abscesses, skin and urinary infections
Dual target (gyrase and topoisomerase IV)	Broader spectrum of action (gram-positive and gram-negative bacteria) and reduced selection of resistance
In vitro activity against MRSA, fluoroquinolone-resistant gram-negative anaerobes	Empirical and targeted use in ABSSSI and potential use in other infections (e.g., respiratory infections, intra-abdominal infections, urinary tract infections)
Mild CYP3A4 induction	No clinically relevant drug–drug interactions
Favorable safety profile in clinical trials	Potential use in infections requiring prolonged treatment (e.g., >2 weeks)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CYP, cytochrome P450; MRSA, methicillin-resistant *Staphylococcus aureus*.

abscesses, and secondary infections such as surgical or burn wound infections and diabetic foot infections.

Efficacy of delafloxacin in ABSSSI has been validated by Phase II and III trials showing comparable activity to linezolid, tigecycline, and vancomycin for the treatment of MDR gram-positive bacteria, including MRSA, and vancomycin/aztreonam against gram-negative bacteria. Compared to vancomycin, delafloxacin appeared more active among obese patients.

The activity against mixed gram-positive and gram-negative infections makes delafloxacin a very attractive option for the treatment of ABSSSI in patients with multiple comorbidities who are at risk of developing polymicrobial infections. Compared to other antibiotics with activity against polymicrobial ABSSSI, such as tigecycline, delafloxacin presents the potential for oral switch, allowing for early patient discharge, and activity against *P. aeruginosa* that can be associated with ABSSSI in selected populations (e.g., patients with diabetes, burn wound infections). Furthermore, compared to linezolid and tigecycline that exhibit bacteriostatic activity, delafloxacin acts as a bactericidal agent.

In diabetic foot infections, moxifloxacin has been found to maintain antimicrobial concentrations above MIC in the perinecrotic tissue, thus proving its effectiveness in patients with extensive ischemic involvement or large ulcers. Similar to moxifloxacin, delafloxacin represents a promising option in these infections due to its diffusion in acidic environments and its broad spectrum of activity.[60,61] Furthermore, the high bone concentrations displayed by quinolones in general and delafloxacin diffusion through the biofilm support further investigation on the use of delafloxacin in ABSSSI complicated by osteomyelitis or bone infections, including prosthetic joint infections.[62] In these settings, where prolonged antimicrobial treatment is usually required, delafloxacin may represent an attractive alternative due to the availability of an oral formulation and a favorable safety profile.

Delafloxacin use in other infections

High pulmonary diffusion (including high penetration in the epithelial lining fluid) along with delafloxacin increased efficacy against MRSA and anaerobes justify its use in respiratory infections, including nosocomial pnemonia and pulmonary abscesses.[46,63] So far, delafloxacin has been successful in treating COPD exacerbations in comparison with levofloxacin and is currently being tested in CA pneumonia with moxifloxacin or linezolid as comparators.[54,55]

The high concentration of quinolones in the urinary tract and prostate tissue makes delafloxacin a potential option for sequential therapy of complicated urinary tract infections and prostatitis, which may require prolonged treatment.[64]

Finally, similar to other quinolones such as moxifloxacin, delafloxacin presents a wide spectrum of action and high tissue penetration with lipid solubility and diffusion in acid media, thus supporting a potential role in the treatment of complicated intra-abdominal infections.[65]

Conclusion

Delafloxacin is a new quinolone characterized by a broad spectrum of activity against gram-positive pathogens, such as MRSA, and gram-negative bacteria including quinolone-resistant *Escherichia coli* and *K. pneumoniae*. Delafloxacin has the potential to be used in sequential therapy due to the availability of an oral formulation. Clinical studies have demonstrated excellent results in the treatment of ABSSSI against heterogeneous bacterial populations, showing similar efficacy to comparators such as vancomycin, linezolid, and tigecycline. New studies are ongoing to support the use of delafloxacin in various infections, while real-world data are awaited to consolidate delafloxacin use as the empirical and targeted therapy of ABSSSI, both in the community and in nosocomial settings.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2014;59(2):e10–e52.
2. Hersh AL, Chambers HF, Maselli JH, Gonzales R. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. *Arch Intern Med.* 2008;168(14):1585–1591.
3. Moran GJ, Krishnadasan A, Gorwitz RJ, et al; EMERGEncy ID Net Study Group. Methicillin-resistant *Staphylococcus aureus* infections among patients in the emergency department. *N Engl J Med*. 2006;355(7):666–674.
4. Pallin DJ, Egan DJ, Pelletier AJ, Espinola JA, Hooper DC, Camargo CA Jr. Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant *Staphylococcus aureus*. *Ann Emerg Med*. 2008;51(3):291–298.
5. Moet GJ, Jones RN, Biedenbach DJ, Stilwell MG, Fritsche TR. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY Antimicrobial Surveillance Program (1998–2004). *Diagn Microbiol Infect Dis*. 2007;57(1):7–13.
6. Bassetti M, Nicco E, Mikulska M. Why is community-associated MRSA spreading across the world and how will it change clinical practice? *Int J Antimicrob Agents.* 2009;34(Suppl 1):S15–S19.
7. European Centre for Disease Prevention and Control, ECDC. Antimicrobial resistance surveillance in Europe 2016. Available from: https://ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data. Acccessed November 30, 2017.
8. Kluytmans-Vandenbergh MF, Kluytmans JA. Community-acquired methicillin-resistant *Staphylococcus aureus*: current perspectives. *Clin Microbiol Infect*. 2006;12(Suppl 1):9–15.
9. David MZ, Daum RS. Community-associated methicillin-resistant *Staphylococcus aureus:* epidemiology and clinical consequences of an emerging epidemic. *Clin Microbiol Rev*. 2010;23(3):616–687.
10. Frazee BW, Lynn J, Charlebois ED, Lambert L, Lowery D, Perdreau-Remington F. High prevalence of methicillin-resistant *Staphylococcus aureus* in emergency department skin and soft tissue infections. *Ann Emerg Med*. 2005;45(3):311–320.
11. Miller LG, Quan C, Shay A, et al. A prospective investigation of outcomes after hospital discharge for endemic, community-acquired methicillin-resistant and -susceptible *Staphylococcus aureus* skin infection. *Clin Infect Dis*. 2007;44(4):483–492.
12. Edelsberg J, Berger A, Weber DJ, Mallick R, Kuznik A, Oster G. Clinical and economic consequences of failure of initial antibiotic therapy for hospitalized patients with complicated skin and skin-structure infections. *Infect Control Hosp Epidemiol*. 2008;29(2):160–169.
13. Bassetti M, Righi E, Carnelutti A. New therapeutic options for skin and soft tissue infections. *Curr Opin Infect Dis*. 2016;29(2):99–108.
14. Stenstrom R, Grafstein E, Romney M, et al. Prevalence of and risk factors for methicillin-resistant Staphylococcus aureus skin and soft tissue infection in a Canadian emergency department. *CJEM*. 2009;11(5):430–438.
15. Cadena J, Richardson AM, Frei CR. Risk factors for methicillin-resistant *Staphylococcus aureus* skin and soft tissue infection in MRSA-colonized patients discharged from a Veterans Affairs hospital. *Epidemiol Infect*. 2016;144(3):647–651.
16. Dryden M, Andrasevic AT, Bassetti M, et al. A European survey of antibiotic management of methicillin-resistant *Staphylococcus aureus* infection: current clinical opinion and practice. *Clin Microbiol Infect*. 2010;16(Suppl 1):3–30.
17. Dryden M, Andrasevic AT, Bassetti M, et al. Managing skin and soft-tissue infection and nosocomial pneumonia caused by MRSA: a 2014 follow-up survey. *Int J Antimicrob Agents*. 2015;45(Suppl 1):S1–S14.
18. Brink AJ. Does resistance in severe infections caused by methicillin-resistant *Staphylococcus aureus* give you the 'creeps'? *Curr Opin Crit Care.* 2012;18(5):451–459.
19. Kim SH, Kim KH, Kim HB, et al. Outcome of vancomycin treatment in patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2008;52(1):192–197.
20. Stryjewski ME, Szczech LA, Benjamin DK Jr, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2007;44(2):190–196.
21. Ye ZK, Li C, Zhai SD. Guidelines for therapeutic drug monitoring of vancomycin: a systematic review. *PLoS One* 2014;9(6):e99044.
22. Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM. Quinolones in 2005: an update. *Clin Microbiol Infect*. 2005;11(4):256–280.
23. Kocsis B, Domokos J, Szabo D. Chemical structure and pharmacokinetics of novel quinolone agents represented by avarofloxacin, delafloxacin, finafloxacin, zabofloxacin and nemonoxacin. *Ann Clin Microbiol Antimicrob*. 2016;15(1):34.
24. De Souza MV. New fluoroquinolones: a class of potent antibiotics. *Mini Rev Med Chem*. 2005;5(11):1009–1017.
25. Piddock LJV. Fluoroquinolone resistance. *BMJ.* 1998;317(7165):1029–1030.
26. Walsh CT, Wencewicz TA. Prospects for new antibiotics: a molecule-centered perspective. *J Antibiot (Tokyo)*. 2014;67(1):7–22.
27. Remy JM, Tow-Keogh CA, McConnell TS, Dalton JM, Devito JA. Activity of delafloxacin against methicillin-resistant *Staphylococcus aureus*: resistance selection and characterization. *J Antimicrob Chemother*. 2012;67(12):2814–2820.
28. Lemaire S, Tulkens PM, Van Bambeke F. Contrasting effects of acidic pH on the extracellular and intracellular activities of the anti-Gram-positive fluoroquinolones moxifloxacin and delafloxacin against *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2011;55(2):649–658.
29. Aldred KJ, Kerns RJ, Osheroff N. Mechanism of quinolone action and resistance. *Biochem.* 2014;53(10):1565–1574.
30. Harnett SJ, Fraise AP, Andrews JM, Jevons G, Brenwald NP, Wise R. Comparative study of the in vitro activity of a new fluoroquinolone, ABT-492. *J Antimicrob Chemother*. 2004;53(5):783–792.
31. Nilius AM, Shen LL, Hensey-Rudloff D, et al. In vitro antibacterial potency and spectrum of ABT-492, a new fluoroquinolone. *Antimicrob Agents Chemother*. 2003;47(10):3260–3269.
32. McCurdy S, Lawrence L, Quintas M, et al. In vitro activity of delafloxacin and microbiological response against fluoroquinolone-susceptible and nonsusceptible *Staphylococcus aureus* isolates from two phase 3 studies of acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother.* 2017;61(9):e00772-17.
33. Almer LS, Hoffrage JB, Keller EL, Flamm RK, Shortridge VD. In vitro and bactericidal activities of ABT-492, a novel fluoroquinolone, against Gram-positive and Gram-negative organisms. *Antimicrob Agents Chemother*. 2004;48(7):2771–2777.
34. Waites KB, Crabb DM, Duffy LB. Comparative in vitro susceptibilities and bactericidal activities of investigational fluoroquinolone ABT-492 and other antimicrobial agents against human mycoplasmas and ureaplasmas. *Antimicrob Agents Chemother*. 2003;47(12):3973–3975.
35. Soge OO, Salipante SJ, No D, Duffy E, Roberts MC. In vitro activity of delafloxacin against clinical *Neisseria gonorrhoeae* isolates and selection of gonococcal delafloxacin resistance. *Antimicrob Agents Chemother*. 2016;60(5):3106–3111.
36. Lemaire S, Tulkens PM, Van Bambeke F. Contrasting effects of acidic pH on the extracellular and intracellular activities of the anti-gram-positive fluoroquinolones moxifloxacin and delafloxacin against *Staphylococcus aureus*. *Antimicrob Agents Chemother.* 2011;55(2):649–658.
37. So W, Crandon JL, Nicolau DP. Effects of urine matrix and pH on the potency of delafloxacin and ciprofloxacin against urogenic *Escherichia coli* and *Klebsiella pneumoniae. J Urol*. 2015;194(2):563–570.

38. Bauer J, Siala W, Tulkens PM, Van Bambeke F. A combined pharmacodynamic quantitative and qualitative model reveals the potent activity of daptomycin and delafloxacin against *Staphylococcus aureus* biofilms. *Antimicrob Agents Chemother*. 2013;57(6):2726–2337.
39. Hoover R, Hunt T, Benedict M, et al. Safety, tolerability, and pharmacokinetic properties of intravenous delafloxacin after single and multiple doses in healthy volunteers. *Clin Ther*. 2016;38(1):53–65.
40. McEwen A, Lawrence L, Hoover R, et al. Disposition, metabolism and mass balance of delafloxacin in healthy human volunteers following intravenous administration. *Xenobiotica*. 2015;45(12):1054–1062.
41. Delafloxacin prescribing information. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208610s000,208611s000lbl.pdf. Accessed December 10, 2017.
42. Hoover R, Hunt T, Benedict M, et al. Single and multiple ascending dose studies of oral delafloxacin: effects of food, sex, and age. *Clin Ther*. 2016;38(1):39–52.
43. Hoover R, Lawrence L, Smith C, Longcor J. Pharmacokinetics (PK) of delafloxacin in patients with varying degrees of renal impairment. Presented at: 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 10–13, 2013; CO, USA. Abstract A-017E.
44. Hoover R, Marbury TC, Preston RA, et al. Clinical pharmacology of delafloxacin in patients with hepatic impairment. *J Clin Pharmacol*. 2017;57(3):328–335.
45. Paulson SK, Wood-Horrall RN, Hoover R, Quintas M, Lawrence LE, Cammarata SK. The pharmacokinetics of the CYP3A substrate midazolam after steady-state dosing of delafloxacin. *Clin Ther*. 2017;39(6):1182–1190.
46. Lepak AJ, Andes DR. In vivo pharmacodynamic target assessment of delafloxacin against *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Klebsiella pneumoniae* in the murine lung infection model. *Antimicrob Agents Chemother*. 2016;60(8):4764–4769.
47. Burak E, Bortolon E, Molstad D, et al. Pharmacokinetics and pharmacodynamics of delafloxacin in *S. aureus* murine thigh infection models. Presented at: 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 12–15, 2009; CA, USA. Poster A1–1941.
48. O'Riordan W, Mehra P, Manos P, Kingsley J, Lawrence L, Cammarata S. A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. *Int J Infect Dis*. 2015;30:67–73.
49. Kingsley J, Mehra P, Lawrence LE, et al. A randomized, double-blind, phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin. *J Antimicrob Chemother*. 2016;71(3):821–829.
50. Melinta Therapeutics, Inc. A phase 3, multicenter, randomized, double-blind, active-controlled study to evaluate the efficacy and safety of delafloxacin compared with vancomycin plus aztreonam in patients with acute bacterial skin and skin structure infections. Available from: https://clinicaltrials.gov/ct2/show/NCT01811732. NML Identifier: NCT01811732. Accessed December 10, 2017.
51. Melinta Therapeutics, Inc. A phase 3, multicenter, randomized, double-blind, active controlled study to evaluate the efficacy and safety of IV and oral delafloxacin compared with vancomycin plus aztreonam in patients with acute bacterial skin and skin structure infections. Available from: https://clinicaltrials.gov/ct2/show/NCT01984684. NML Identifier: NCT01984684. Accessed December 10, 2017.
52. O'Riordan W, Overcash S, Lawrence L, McCurdy SP, Tseng C, Cammarata SK. Outcomes with IV/oral delafloxacin compared to vancomycin/aztreonam in treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) and gram-negative pathogens. Presented at: IDWeek 2017; San Diego, CA, USA. Poster 1856.
53. Overcash S, O'Riordan W, Lawrence L, McCurdy SP, Tseng C, Cammarata SK. Outcomes with IV/oral delafloxacin compared to vancomycin/aztreonam in treatment of patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Gram-positive pathogens. Presented at: IDWeek 2017; San Diego, CA, USA. Poster 1857.
54. Longcor J, Hopkins S, Wikler M, Lawrence L. A phase 2 safety and efficacy study of oral delafloxacin in subjects with acute bacterial exacerbation of chronic bronchitis (ABECB). Presented at: ID Week 2012; San Diego, CA, USA.
55. Melinta Therapeutics, Inc. A phase 3, multicenter, randomized, double-blind, comparator-controlled study to evaluate the safety and efficacy of intravenous to oral delafloxacin in adult subjects with community-acquired bacterial pneumonia. Available from: https://clinicaltrials.gov/ct2/show/NCT02679573. NML Identifier: NCT02679573. Accessed December 10, 2017.
56. Corey GA, Hooper D, Lodise TP, Tseng C, Cammarata SK. Comparison of safety profile of delafloxacin versus vancomycin/aztreonam in the treatment of patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSI): integrated safety findings from two phase III studies. Presented at: IDWeek 2017; San Diego, CA, USA. Poster 1858.
57. Pullman J, Gardovskis J, Farley B, et al. Efficacy and safety of delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a Phase 3, double-blind, randomized study. *J Antimicrob Chemother*. 2017;72(12):3471–3480.
58. Melinta Therapeutics. Assessment of phototoxicity potential of delafloxacin in healthy male and female subjects: a Phase 1 study. Presented at: 55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 17–21, 2015; CA, USA. Abstract F-1198A.
59. Litwin JS, Benedict MS, Thorn MD, Lawrence LE, Cammarata SK, Sun E. A thorough QT study to evaluate the effects of therapeutic and supratherapeutic doses of delafloxacin on cardiac repolarization. *Antimicrob Agents Chemother*. 2015;59(6):3469–3473.
60. Lipsky BA, Giordano P, Choudhri S, Song J. Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin-tazobactam/amoxicillin-clavulanate. *J Antimicrob Chemother*. 2007;60(2):370–376.
61. Majcher-Peszynska J, Sass M, Schipper S, et al; Moxifloxacin-DFI Study Group. Pharmacokinetics and penetration of moxifloxacin into infected diabetic foot tissue in a large diabetic patient cohort. *Eur J Clin Pharmacol*. 2011;67(2):135–142.
62. Rimmele T, Boselli E, Breilh D, et al. Diffusion of levofloxacin into bone and synovial tissues. *J Antimicrob Chemother*. 2004;53(3):533–535.
63. Thabit AK, Crandon JL, Nicolau DP. Pharmacodynamic and pharmacokinetic profiling of delafloxacin in a murine lung model against community-acquired respiratory tract pathogens. *Int J Antimicrob Agents*. 2016;48(5):535–541.
64. Charalabopoulos K, Karachalios G, Baltogiannis D, Charalabopoulos A, Giannakopoulos X, Sofikitis N. Penetration of antimicrobial agents into the prostate. *Chemotherapy*. 2003;49(6):269–279.
65. Malangoni MA, Song J, Herrington J, Choudhri S, Pertel P. Randomized controlled trial of moxifloxacin compared with piperacillin–tazobactam and amoxicillin–clavulanate for the treatment of complicated intra-abdominal infections. *Ann Surg*. 2006;244(2):204–211.