Possible Role for the New Fluoroquinolones (Levofloxacin, Grepafloxacin, Trovafloxacin, Clinafloxacin, Sparfloxacin, and DU-6859a) in the Treatment of Anaerobic Infections: Review of Current Information on Efficacy and Safety

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The currently available fluoroquinolones have modest activity against anaerobes. Newer fluoroquinolones with increased in vitro activity against anaerobes are under development and include levofloxacin, clinafloxacin, trovafloxacin, grepafloxacin, and DU-6859a. Side effects of the quinolones have varied according to the specific compounds and include central nervous system stimulation, gastrointestinal disturbances, vasculitis, and photosensitization. Monitoring for toxicity is incompletely reliable in identifying all potential serious side effects such as the "temafloxacin syndrome." Other fluoroquinolones may produce this syndrome rarely or not at all. In this paper, I review limited published studies on the use of these agents for skin and skin-structure infections and gynecologic infections. Studies in progress are noted, and when available, in vitro data on the efficacy of these agents against bacterial isolates from specific sources are reviewed and evaluated in terms of potential clinical utility.

Resistance of anaerobic bacteria to all antimicrobial agents including β-lactams, β-lactamase inhibitor combinations, carbapenems, and metronidazole has been reported with increasing frequency [1]. Consequently, there is a need to find new agents active against anaerobic bacteria or to improve the activity of available agents. It would be useful to have oral antimicrobial agents with broad-spectrum activity against both aerobes and anaerobes in order to provide therapeutic options other than multiple (usually iv) agents.

The fluoroquinolones are synthetic, heteroaromatic, bicyclic compounds that have excellent activity against many aerobic bacteria, but they have only modest-to-poor activity against anaerobes [2]. Several new fluoroquinolones with improved in vitro anaerobic activity have been synthetized and some of these agents are currently undergoing clinical trials.

In this paper, I review published studies on the efficacy of the currently marketed fluoroquinolones against anaerobic infections, and I provide an update on the status of the new fluoroquinolones that are under development and are undergoing clinical trials in situations where anaerobes are potential pathogens. I will discuss the in vitro activity of selected compounds (for which only in vitro data are available) against specific anaerobic pathogens isolated from known sources and use this data to determine the potential clinical usefulness of these compounds.

Ciprofloxacin

Ciprofloxacin was first introduced in the United States in 1988 and was the first fluoroquinolone indicated for infections outside the urinary tract. Ciprofloxacin has a cyclopropyl group attached to the N-1 position, a fluorine at the C-6 position, and a piperaznyl group at the C-7 position. At the time of its introduction, ciprofloxacin was considered a major advance in therapy for aerobic gram-negative infections; however, the drug was noted to have relatively poor activity against anaerobes [2, 3]. In a 1989 summary of the worldwide experience with ciprofloxacin, Neu [4] noted eight instances in which anaerobic infections were not eradicated by iv ciprofloxacin; this author also noted that in four of seven instances, anaerobic infection was eradicated by a combination of oral and iv ciprofloxacin. No other details of these cases were given.

In most instances in which ciprofloxacin has been used for infections where anaerobes were potential or actual pathogens, most clinicians have added a second agent (e.g., metronidazole or clindamycin) to the regimen. Fass [5] used oral ciprofloxacin to treat 30 patients with soft-tissue infections, including two patients with infections due to Bacteroides species and three with infections due to peptostreptococci; all of these organisms were eradicated. Wood and Logan [6] used the drug to treat 21 patients with soft-tissue infections; one of these patients had ischemic disease and a mixed Escherichia coli and Bacteroides fragilis infection for which ciprofloxacin therapy failed.

In a prospective, controlled, nonblind randomized study, Crombleholme et al. [7] noted that ciprofloxacin was less effective than clindamycin plus gentamicin in the treatment of acute pelvic inflammatory disease because ciprofloxacin failed to eradicate anaerobes, especially Bacteroides species (including organisms now classified as Prevotella and Porphyromonas species).

Ciprofloxacin was found to be safe and well tolerated, with a 5%–10% incidence of side effects; it was necessary to discontinue therapy in only 2%–10% of cases [3, 8]. The most common side effects were gastrointestinal complaints (2%–8% of patients) consisting mainly of nausea, emesis, abdominal pain,
diarrhea, and anorexia (≤10% of patients), followed by CNS excitatory effects (0.4%–4.4%) such as anxiety, insomnia, euphoria, and rarely, seizures and hallucinations (1%–4%). Hypersensitivity reactions occurred in 1% (0.4%–1.0%) of patients. Abnormal laboratory data, especially elevation of serum transaminase levels, were observed for ~4% of patients treated with ciprofloxacin.

**Ofloxacin**

Ofloxacin is a 4-methyl-1-piperazinyl fluoroquinolone with a fused oxazine ring that connects the N-1 and C-8 positions. This agent was noted to have enhanced activity against anaerobic bacteria when it was compared with ciprofloxacin and norfloxacin [2]; however, it was clinically evaluated primarily in patients with aerobic bacterial infections [9, 10].

The results of noncomparative studies performed in Japan from 1981 to 1983, among patients with a variety of infections including skin and soft-tissue infections, cutaneous abscesses, and phlegmons indicated that ofloxacin was effective in patients whose infecting flora included Veillonella species and Peptostreptococcus species [9]. Graninger et al. [10] studied the efficacy of iv ofloxacin in 70 patients with a variety of infections including skin and soft-tissue infections (33 patients) and intra-abdominal abscesses (14). Only two patients had anaerobes cultured from their wounds: one patient had a furuncle, and one had a sacral dermoid cyst; cultures of specimens from both patients yielded a Bacteroides species and a Peptostreptococcus species. Both patients were considered nonevaluable.

Gentry et al. [11] reported the results of a study of oral ofloxacin vs. intravenous cefotaxime for the treatment of 100 successive patients with skin infections and skin-structure infections. Three patients in the cefotaxime group and one patient in the ofloxacin group had Bacteroides species cultured from their wounds. All of these organisms were eradicated during therapy.

One of my colleagues and I [12] studied the in vitro activity of ofloxacin against 177 isolates recovered from intra-abdominal infections. We found that some B. fragilis strains were susceptible to ofloxacin at an MIC of 4 μg/mL but that strains of Bacteroides thetaiotaomicron and Bacteroides ovatus were resistant to ofloxacin (MIC₉₀, 16 μg/mL and 32 μg/mL, respectively). Isolates associated with female genital tract infections such as Prevotella intermedia, Prevotella melaninogenica, Prevotella bivia, Peptostreptococcus asaccharolytica, and all peptostreptococci were susceptible to ofloxacin.

In a study of 194 aerobic and anaerobic isolates recovered from bite wound infections, my colleagues and I [13] found ofloxacin to be active against all aerobic and anaerobic isolates at ≤4 μg/mL, with the exception of fusobacteria, for which the MIC₉₀ was 64 μg/mL.

The safety of ofloxacin was evaluated after more than 1.5 million courses of therapy [9, 14]; the incidence of side effects was low, ranging from 2.5%–8.5% among treated patients. During clinical trials that included ~16,000 patients, gastrointestinal symptoms occurred in 2.6%–3.5% of patients, CNS events occurred in 0.9%–4.6%, and hypersensitivity occurred in 0.5%.

**Levofloxacin**

Levofloxacin is the L-isomer of ofloxacin and possesses increased in vitro antibacterial activity against a variety of bacteria including anaerobes [15, 16]. Levofloxacin is currently under clinical investigation in a variety of studies (M. Corrado, personal communication).

Levofloxacin has been studied as treatment for complicated skin infections and skin-structure infections including diabetic foot infections, osteomyelitis, and decubitus ulcers. To date, 43 patients with evaluable bacteriologically proven anaerobic infections (all skin and soft-tissue infections) have been treated with levofloxacin in the United States. The following pathogens have been recovered: Bacteroides/Prevotella species (14 patients); clostridia (2); fusobacteria (4); peptostreptococci (17); and Propionibacterium species (2).

The eradication rate was 100% (17 of 17 cases) for infections due to peptostreptococci; 79% (11 of 14) for infections due to Bacteroides/Prevotella species; and 92% (11 of 12) for cases due to the other anaerobic isolates. Failure of eradication was observed in one case each due to the following organisms: Gemella morbillorum (MIC, 0.25 μg/mL), P. bivia (MIC, 1 μg/mL), B. fragilis (zone of inhibition, 26 mm), and unnamed Bacteroides species (zone of inhibition, 28 mm).

Yamada et al. [17] studied 24 patients with a variety of gynecologic infections (i.e., endometritis [14], adnexitis [3], and abscesses of Bartholin’s gland [7]) who received levofloxacin at a daily dose of 300 mg for 5–7 days. These authors reported that the clinical efficacy rate was 95.8% and that a superinfection occurred in 2 of 14 bacteriologically evaluable patients. The specific bacteriology of these infections was not reported.

Other clinical studies of levofloxacin that have been performed (M. Corrado, personal communication) but not yet analyzed include studies of pneumonia (clinical treatment failure was noted for several patients with pneumonia due to F. nucleatum) and studies of sinusitis that required antral puncture for bacteriologic evaluation (specimens were not cultured for anaerobes even though anaerobes are often potential pathogens of chronic sinusitis).

In a microbiological study of 194 aerobic and anaerobic isolates recovered from bite wound infections, my colleagues and I [18] found levofloxacin to be active against all aerobic isolates at ≤1 μg/mL and all anaerobic isolates at ≤4 μg/mL; however, fusobacteria were often resistant to this agent. The proposed breakpoint for levofloxacin is ≤2 μg/mL for fully susceptible isolates, 4 μg/mL for intermediately susceptible isolates, and ≥8 μg/mL for resistant isolates.
The safety of levofloxacin has been noted (M. Corrado, personal communication) in the current studies, and the approximate incidence of side effects is as follows: headache, 5% of patients; insomnia, 2%; nausea, 3%–5%; emesis, 0.5%; and metallic taste, <0.5%. All other side effects, including seizures (<1 patient per 1,000,000 treated), vasculitis, and psychosis, were rare. Phototoxicity has been observed in <1% of patients (one of 3,500) and is usually mild.

**Sparfloxacin**

Sparfloxacin is characterized by an amino moiety at the 5 position, a fluorene at both the 6 and 8 positions, and a 5-dimethyl-piperazinyl group at the 7 position. This drug’s in vitro activity against isolates from the United States and Europe are reviewed in this symposium by Hecht [19] and Nord [20], respectively. In prior studies, sparfloxacin was found to inhibit most anaerobes at ≤2 µg/mL [2, 14]; the MIC₉₀ for various members of the *B. fragilis* group has ranged from 4 µg/mL to 8 µg/mL [2]. In addition, strains of *P. bivia*, *Fusobacterium varium*, and *P. melanigenica* may require 8–16 µg/mL of this drug for inhibition [2]. A breakpoint of 2 µg/mL has been proposed.

Watanabe et al. [21] reported the efficacy of sparfloxacin in 82 patients (60 males and 22 females) with skin and skin-structure infections associated with surgery. Patients received 200 mg once daily (58 patients), 300 mg once daily (13), or 150 mg twice daily (11) for 4–12 days. While some details for each treatment group were not reported, these authors noted the following clinical efficacy rates. Overall, 11 (84.6%) of 13 patients with periprosthetic abscess responded (6 of 8 patients received 200 mg/d and 5 of 5 received 300 mg/d); the efficacy rate was 90.9% (10 of 11) when surgery was performed but only 50% (1 of 2) when surgery was not performed. Eleven (100%) of 11 patients with unspecified wound infections responded, including those who received either the 200 mg/d regimen or the 300 mg/d regimen (10 underwent surgery, and one did not). Overall, 11 (84.6%) of 13 patients with subcutaneous abscesses responded (all of these patients underwent surgery, 10 of 11 received the 200 mg/d regimen, while 1 of 2 received 30 mg/d). Five (83.3%) of six patients with cellulitis responded. All of the 23 strains of anaerobes isolated (including 11 peptostreptococci and four *B. fragilis* group species) were eradicated.

Takahashi et al. [22] studied 179 patients with skin infections and soft-tissue infections who received 100 mg or 200 mg of sparfloxacin once or twice daily for 7–10 days. Sixteen anaerobes (genus and species not specified) were isolated from the diverse group of infections studied, and 15 (93.8%) of 16 pathogens were eradicated.

In a microbiological study of 25 consecutive diabetic patients with foot infections, my colleagues and I [23] evaluated the in vitro activity of sparfloxacin (breakpoint, 4 µg/mL) and found that 12% of the 113 isolates (including two *Bacteroides ovatus* isolates) were resistant to sparfloxacin and that 36% of the patients were infected with at least one sparfloxacin-resistant isolate—often an enterococcus or *Staphylococcus aureus*.

In two studies of different strains of aerobic and anaerobic organisms isolated from bite wound infections, my colleagues and I [18, 24] found that sparfloxacin was active against all aerobic isolates (MIC, ≤1.0 µg/mL) and against most anaerobic isolates with the exception of fusobacteria.

Matsuda et al. [25] studied 201 patients with various gynecologic infections who received 200–300 mg of sparfloxacin once or twice daily for 7 days (“in principle”) and reported an overall cure rate of 96.5% and a bacteriologic eradication rate of 97.2% for the 35 unspecified anaerobic bacteria isolated.

There are currently a number of active sparfloxacin studies under way that are either not yet published or have not yet been completed and analyzed (G. Talbot, personal communication). These trials include two studies of community-acquired pneumonia (330 patients and 430 patients have been enrolled to date) in which expectorated sputum is being analyzed to determine the efficacy of sparfloxacin. Although some of these pneumonias may be due to multiple bacteria and may involve anaerobes, the sputum specimens are not being cultured for anaerobes; therefore, no such data is expected to be forthcoming.

A skin and skin-structure study involving ~600 patients is under way and may yield some data about sparfloxacin’s efficacy against a limited number of anaerobes, including those that cause diabetic foot infections. Two studies of sinusitis (~250 patients have been enrolled) are being conducted. To date, a culture for one patient has yielded *F. nucleatum*, and treatment with sparfloxacin has failed clinically.

Sparfloxacin’s toxicity has included photosensitization (2%–11.7% of patients) after exposure to direct and reflected sunlight, in cloudy weather, or through glass (Investigator’s Brochure). The use of sunscreen has been of limited benefit. In addition to the usual fluoroquinolone-related side effects (diarrhea [2.5% of patients], headache [1.4%], and nausea [1.7%]), prolongation of the QT interval was observed; the rate was 90.9% (10 of 11) when surgery was performed but only 50% (1 of 2) when surgery was not performed. Eleven (100%) of 11 patients with unspecified wound infections responded, including those who received either the 200 mg/d regimen or the 300 mg/d regimen (10 underwent surgery, and one did not). Overall, 11 (84.6%) of 13 patients with subcutaneous abscesses responded (all of these patients underwent surgery, 10 of 11 received the 200 mg/d regimen, while 1 of 2 received 30 mg/d). Five (83.3%) of six patients with cellulitis responded. All of the 23 strains of anaerobes isolated (including 11 peptostreptococci and four *B. fragilis* group species) were eradicated.

**Trovafloxacin**

Trovafloxacin (CP-99,219) is a trifluoronaphthyridone with a 7-(3-azabicyclo[3.1.0]hexyl) group. It has shown good activity against anaerobes in vitro [26–28] and is currently undergoing clinical trials (T. Gootz, personal communication). Girard et al. [29] used the CF1 (Charles River) mixed-sex mouse model to perform two studies. The first study involved the activity of trovafloxacin against mixed infections with *B. fragilis* (ATCC [American Type Culture Collection] 25285) and *S. aureus*. Sterilized paper disks inoculated with a 1:1 mixture of *B. fragilis* (1 × 10⁶ cfu/disk) and *S. aureus* (4 × 10⁵ cfu/disk) were
implanted on the left midback of each mouse. The mice were treated beginning 24 hours after challenge with either oral trovafloxacin (100 mg/kg) or oral ciprofloxacin (100 mg/kg). Ciprofloxacin therapy resulted in a similar cfu per disk as that found for untreated controls. Trovafloxacin reduced the cfu of *S. aureus* by ~1,000-fold and the cfu of *B. fragilis* by >10,000-fold.

In the second study, the mice were inoculated in a similar manner with *E. coli* (3 × 10^3 cfu/disk) and *B. fragilis* (1.6 × 10^6 cfu/disk), and either trovafloxacin (100 mg/kg) or ciprofloxacin (100 mg/kg) were administered intraperitoneally. Trovafloxacin reduced the numbers of recoverable *B. fragilis* (2.65 ± 0.36 log_{10} cfu/disk) and *E. coli* (3.79 ± 0.67 log_{10} cfu/disk), whereas the numbers of recoverable *B. fragilis* (7.28 ± 0.54 log_{10} cfu/disk) and *E. coli* (6.63 ± 0.50 log_{10} cfu/disk) were not reduced in controls.

Ciprofloxacin was ineffective in reducing the numbers of bacteria, which were similar to those observed for the control groups. Girard et al. note that a relatively high dose of trovafloxacin was used in these studies and that in later dose-titration studies (data not shown), the results were comparable with a dose of 25 mg/kg.

Toxicity studies of trovafloxacin have shown an increased incidence and intensity of lightheadedness, headache, nausea, and emesis when a single oral dose is increased from 30 mg to 1,000 mg and when multiple oral doses are increased from 100 mg to 300 mg daily (Investigator’s Brochure). Other reported events have included sweating, facial flushing, abdominal cramping, and rash and pruritus; phlebitis has also occurred with intravenous infusion of the drug.

**Grepafloxacin**

Grepafloxacin (OPC-17116) is a 1-cyclopropyl, 5-methyl, 7-methylpiperazinyl substituted fluoroquinolone. Matsuda et al. [30] studied 62 patients with mild-to-moderate gynecologic infections (including intrauterine infections) who were receiving oral grepafloxacin (200 mg or 300 mg) once daily for 3–14 days. These authors reported a 94.3% clinical cure rate and a 93% bacteriologic eradication rate for 53 evaluable patients. They did not specify whether any anaerobes were isolated, but the treated infections included Bartholin’s abscess, adnexitis, mastitis, and intrauterine infections, which would be expected to have an anaerobic component in many cases. Side effects included emesis, dizziness, syncope, fatigue, and a medicinal taste (Investigator’s Brochure).

**Clinafloxacin**

Clinafloxacin (CI-960, PD 127391, and AM 1091) is a 1-cyclopropyl, 7-(3-amino-1-pyrrolidinyl), 8-chloroquinolone that is currently undergoing clinical trials for a variety of infections that involve anaerobes (K. Tack, personal communication). The published clinical experience [31] involves 11 patients enrolled in compassionate-use protocols for treatment of serious infections due to multidrug-resistant aerobes.

The findings of currently active studies have not been analyzed. Approximately 150 patients have been enrolled to date in a blinded study of intra-abdominal infection, but the code has not been broken. These patients are receiving either clinafloxacin (200 mg every 12 hours) or imipenem (500 mg every 6 hours). Vancomycin may be added to either regimen for coverage of methicillin-resistant *S. aureus* or enterococci. A study of skin and skin-structure infections is under way but is in the preliminary stages, and no data are available at this time. A study of nosocomial pneumonia is under way, but cultures for anaerobes are not being performed. A study of gynecologic infections is planned, but it is not yet active, and no studies of sinusitis are currently planned.

The toxicity encountered to date with clinafloxacin includes the expected neuroexcitatory events (i.e., anxiety, agitation, tremulousness, confusion, and seizures); photosensitization (14% of patients); and diarrhea, including *Clostridium difficile* colitis (13%) (K. Tack, personal communication, and Investigator’s Brochure). The rates and severity of these side effects will be determined and reported during the ongoing clinical trials. The Investigator’s Brochure notes that in controlled trials of oral and intravenous clinafloxacin, 63% of placebo-treated patients and 87% of clinafloxacin-treated patients reported adverse events. The most common adverse events were vasodilation (33% of patients), dizziness (32%), and headache (27%).

**DU-6859a**

DU-6859a is a [(7S)-amino-5-azaspiro[2, 4]heptan-5-yl]-8-chloro-6-fluoro-1[(1R, 2S)-cis-2-fluoro-1-cyclopropyl]-1,4-dihydro-4-oxoquinolone-3-carboxylic acid [32] with improved in vitro activity against anaerobes [33, 34]. It has been studied in animals (rats, dogs, and monkeys), and its pharmacokinetics have been studied in volunteers [35]. Miyazaki et al. [36] used a murine model to study the efficacy of DU-6859a against a variety of gram-positive and gram-negative aerobes and facultative organisms but not against anaerobes. In this model, DU-6859a was more active on the basis of weight than were several other fluoroquinolones [36]. To date, clinical trials for treatment of active infections have not been initiated.

**Temafloxacin**

Temafloxacin was a substituted fluoroquinolone with a 4-methyl group on the piperazine ring (which improved its lipid solubility) and a 2,4-difluorophenyl group at position 1 (which further modulated its solubility and enhanced its antimicrobial activity against aerobic and anaerobic bacteria) [37–39]. Clinical studies included infections in which anaerobes were potential pathogens, but little specific bacteriologic data from those studies is available.
In initial reports on the safety of temafloxacin [40] in >2,600 patients who received dosages of ≤600 mg twice daily, adverse reactions were noted in 31.5% of patients (this percentage is comparable to that for other fluoroquinolones), and therapy was discontinued in only 3.7%–4.1% of patients. The main side effects were gastrointestinal disturbances (nausea and emesis [~5% of patients]), rash (2%), and CNS stimulation (dizziness and headache [1%–10%]).

The “temafloxacin syndrome” [41] refers to vasculitis with microangiopathic hemolytic anemia, disseminated intravascular coagulation, thrombocytopenia, renal dysfunction, hepatotoxicity, and CNS abnormalities, including stroke. Its incidence was estimated to be 150 cases per 300,000 patients treated; it was not found during clinical trials but became evident during postmarketing surveillance. As a consequence, the manufacturer withdrew temafloxacin from the market.

Other fluoroquinolones may produce this syndrome only rarely or not at all. Still, compounds with similarities in structure, especially the difluorophenyl ring at position 1, are undergoing clinical trials and are being carefully monitored by the U.S. Food and Drug Administration.

Conclusion

The current group of fluoroquinolones that are under various stages of development have improved in vitro activity against anaerobic bacteria and are undergoing clinical evaluation in the treatment of mixed anaerobic infections. To date, the available clinical data are sparse. It is expected that within the next several months to a year, the results of many studies will be reported; these results will ultimately form the basis for the evaluation of the potential clinical utility of the newer fluoroquinolones as therapy for anaerobic infections.

References


