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SUSCEPTIBILITY

In Vitro Activity of Tedizolid Compared to Linezolid and Five Other Antimicrobial Agents against 332 Anaerobic Isolates, Including *Bacteroides fragilis* Group, *Prevotella*, *Porphyromonas*, and *Veillonella* Species

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ABSTRACT Tedizolid's anaerobic activity is unappreciated. In this study, it was active against all 332 anaerobic isolates tested at ≤2 μg/ml except *Bilophila wadsworthia* and was more active than linezolid against *Bacteroides fragilis* group species (MIC_{90}, 1 μg/ml versus 2 to 4 μg/ml). Tedizolid was active against Gram-positive anaerobes (MIC_{90} for clostridia, 0.25 to 1 μg/ml; MIC_{90} for anaerobic cocci, ≤0.06 to 0.25 μg/ml). Our data coupled with clinical reports indicate that clinicians should consider its use in mixed infections where *Staphylococcus aureus* and anaerobes are involved.

KEYWORDS *Bacteroides fragilis*, *Prevotella* spp., *Veillonella* spp., anaerobes, linezolid, tedizolid

Oxazolidinones are primarily thought of as active against Gram-positive aerobes (1, 2). Tedizolid, the newest oxazolidinone, is approved for use in acute bacterial skin and skin structure infections (ABSSSIs) and offers potential advantages of once-a-day dosing, as well as potential decreased toxicities and has activity against linezolid-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) (3–5). There is a paucity of data about the susceptibility of anaerobic bacteria in general, including susceptibility to tedizolid (6, 7). However, the successful clinical use of linezolid in patients with ABSSSIs due to resistant anaerobic bacteria and cases of resistant *Bacteroides fragilis* wound sepsis has been reported (8, 9). We evaluated the comparative activity of tedizolid against a broad range of clinically isolated anaerobic pathogens, including *Fusobacterium*, *Prevotella*, and *Veillonella* spp.

Organisms tested were recovered from clinical samples (generally obtained from 2015 to 2017) from human infections, identified by standard methods (10, 11), and stored at −70°C. Susceptibility testing was performed using supplemented brucella blood agar dilution according to CLSI methods (12).

The antimicrobial agents tested were tedizolid, linezolid, moxifloxacin, ampicillin-sulbactam, piperacillin-tazobactam, clindamycin, and metronidazole. Drugs were reconstituted according to the manufacturers' instructions or the guidelines in CLSI document M11-A9 (12). Piperacillin-tazobactam was tested from 128 μg/ml to 0.06 μg/ml with tazobactam constant at 4 μg/ml; tedizolid was tested at 32 to 0.03 μg/ml and the remainder at 32 to 0.06 μg/ml.

Quality control (QC) strains included *Bacteroides fragilis* ATCC 25285 and *Clostridioides difficile* ATCC 700057. After 36 to 48 h of incubation in the anaerobic chamber at 36°C, the plates were examined for growth. The MIC was defined as the concentration of drug that completely inhibited growth or resulted in a marked reduction relative to

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the drug-free growth control. Breakpoints were interpreted according to CLSI document M100-S30 (13).

The comparative *in vitro* activity (MICs) of tedizolid against 332 anaerobes is presented in Table 1. Tedizolid was active against all 332 anaerobic isolates at ≤2 μg/ml, except for *Bilophila wadsworthia* (MIC_{90}, 16 μg/ml), which was also resistant to linezolid (MIC_{90}, 16 μg/ml), ampicillin-sulbactam, and piperacillin-tazobactam (MIC_{90}, >64 μg/ml) but susceptible to moxifloxacin (MIC_{90}, 0.5 μg/ml) and metronidazole (MIC_{90}, 1 μg/ml). Tedizolid was generally one to four dilutions more active than linezolid, including against *B. fragilis* group species (MIC_{90}, 1 μg/ml versus 2 to 4 μg/ml) and most other Gram-negative anaerobes tested. It was active at <2 μg/ml against 13 *B. fragilis* strains, 8 *Bacteroides thetaiotaomicron* strains, 2 *Bacteroides ovatus* strains, and 1 *Bacteroides uniformis* strain with piperacillin-tazobactam MICs of >16 μg/ml. Clindamycin resistance was common at ~50% or more for *B. fragilis*, *B. uniformis*, and *B. ovatus* isolates and ~30% for *Bacteroides caccae*, *B. thetaiotaomicron*, and *B. vulgatus* isolates. Tedizolid was especially active against Gram-positive anaerobes (MIC_{90} for clostridia, 0.25 to 1 μg/ml; MIC_{90} for cocci, ≤0.06 to 0.25 μg/ml). Moxifloxacin resistance was found in 44% of *B. fragilis* group isolates, including 10% of *B. fragilis* isolates, ~30% of *B. caccae* and *B. thetaiotaomicron* isolates, and ~55% of *B. vulgatus* isolates.

Against *Parabacteroides distasonis*, *P. goldsteinii*, *P. merdae*, and *Veillonella* spp., the tedizolid MIC_{90} was 2 μg/ml. Tedizolid was also active against a variety of *Fusobacterium* spp. (MIC_{90}, ≤0.125 μg/ml) as well as *Porphyromonas* and *Prevotella* (MIC_{90}, ≤1 μg/ml, except for *P. bivia* [MIC_{90}, 4 μg/ml]).

Tedizolid is FDA approved for use in ABSSSIs and is active *in vitro* against clindamycin-, tetracycline-, levofloxacin-, daptomycin-, and tigecycline-resistant MRSA isolates (14–16).

Six days of tedizolid therapy was noninferior to 10 days of linezolid, including an early clinical response at 48 to 72 h (5). A study of 433 patients with diabetic foot infections (DFIs), a subset of ABSSSIs, showed that 83% were polymicrobial and 46% involved anaerobes with 2.7 anaerobic isolates per specimen (17). Gram-positive anaerobic cocci, especially *Finegoldia magna* (22.1%), accounted for 48.2% of the anaerobic isolates along with clostridia (4.4%). *B. fragilis* group species were the most common Gram-negative anaerobes (12.1%) isolated.

Zurenko et al. (18) found variable linezolid activity against 4 strains of *B. fragilis* group species (MIC range, 2 to 16 μg/ml) and 2 strains of *Prevotella* spp. (MIC, 1 μg/ml). Wybo et al. (19) found a linezolid MIC_{90} of 4 μg/ml for *Bacteroides* spp. and *Parabacteroides* spp., while fusobacteria had an MIC_{90} of 1 μg/ml. We previously noted that linezolid had activity against many anaerobic Gram-positive organisms, including *F. magna*, *Peptostreptococcus anaerobius*, *Parvimonas micra* (MIC_{90}, 2 μg/ml; range, 2 to 4 μg/ml), and *Peptoniphilus asaccharolyticus* (MIC_{90}, 1 μg/ml) (20).

Lee et al. (16) found that tedizolid had MICs 4- to 8-fold lower than those of linezolid. Similarly, Schaadt et al. (21) reported that tedizolid had up to 4-fold better activity than linezolid against *Bacteroides* spp. (MIC_{90} range, 2 to 8 μg/ml).

Previously (7), tedizolid's *in vitro* activity against *B. fragilis* was found to be equivalent to (*B. fragilis*, *B. ovatus*, and *B. vulgatus*) to 2- to 4-fold greater (*B. thetaiotaomicron*) than linezolid's. Our study confirms the improved comparative *in vitro* activity of tedizolid versus linezolid against a broader range of anaerobes with improved activity against Gram-negative anaerobes, including *Fusobacterium* spp., *Prevotella* spp., and *Veillonella* spp. *Prevotella bivia* had an MIC_{90} of 4 μg/ml, which was higher than that of other *Prevotella* spp. (MIC_{90}, 1 μg/ml). Schaadt et al. (21) found *Prevotella* to have an MIC_{90} of 4 μg/ml (range, ≤0.016 to 16 μg/ml). *Veillonella* spp., emerging pathogens which are not often tested, had a tedizolid MIC_{90} of 1 μg/ml.

A U.S. soldier in Afghanistan injured by an improvised explosive device (IED) developed *B. fragilis* sepsis and a leg infection resistant to all usual anaerobic agents but was treated and cured with a combination of linezolid and moxifloxacin (7). A case of *B. fragilis* sepsis resistant to metronidazole, beta-lactam–beta-lactamase inhibitors, and carbapenems was successfully treated with linezolid (8). These cases suggest a possible

TABLE 1 Comparative *in vitro* activity of tedizolid compared to linezolid and 5 other agents against 332 anaerobic isolates, including *Bacteroides fragilis* group species

Organism (no. of isolates) and agent	MIC (μg/ml)		
	Range	50%	90%
Bacteroides caccae (11)			
Tedizolid	0.25–1	1	1
Linezolid	1–4	2	4
Ampicillin-sulbactam	0.5–8	1	4
Piperacillin-tazobactam	0.5–8	2	8
Moxifloxacin	0.25–16	2	16
Clindamycin	≤0.06–>32	1	>32
Metronidazole	0.25–1	0.5	1
Bacteroides fragilis (46)			
Tedizolid	0.5–2	1	1
Linezolid	2–16	4	4
Ampicillin-sulbactam	0.5–>64	16	64
Piperacillin-tazobactam	≤0.03–>64	4	>64
Moxifloxacin	0.125–>16	0.5	8
Clindamycin	≤0.06–>32	0.5	>32
Metronidazole	0.25–32	1	1
Bacteroides ovatus (11)			
Tedizolid	1–2	1	1
Linezolid	2–4	2	2
Ampicillin-sulbactam	1–32	4	16
Piperacillin-tazobactam	2–>64	4	32
Moxifloxacin	0.5–>16	1	8
Clindamycin	0.125–>32	2	>32
Metronidazole	0.25–2	1	1
Bacteroides thetaiotaomicron (14)			
Tedizolid	1–1	1	1
Linezolid	2–4	2	4
Ampicillin-sulbactam	1–32	4	16
Piperacillin-tazobactam	8–>64	16	>64
Moxifloxacin	0.5–16	1	16
Clindamycin	0.25–>32	4	>32
Metronidazole	0.25–2	0.5	1
Bacteroides uniformis (11)			
Tedizolid	0.5–1	0.5	1
Linezolid	1–2	2	2
Ampicillin-sulbactam	1–32	8	16
Piperacillin-tazobactam	0.5–>64	2	4
Moxifloxacin	0.25–>16	4	16
Clindamycin	≤0.06–>32	>32	>32
Metronidazole	0.25–1	0.5	1
Bacteroides vulgatus (15)			
Tedizolid	0.25–2	1	1
Linezolid	1–2	2	2
Ampicillin-sulbactam	0.5–16	4	16
Piperacillin-tazobactam	0.125–4	4	4
Moxifloxacin	0.125–>16	16	>16
Clindamycin	≤0.06–>32	>32	>32
Metronidazole	0.125–2	0.5	2
Bilophila wadsworthia (11)			
Tedizolid	>16–>16	>16	>16
Linezolid	4–16	16	16
Ampicillin-sulbactam	2–>64	64	>64
Piperacillin-tazobactam	4–>64	>64	>64
Moxifloxacin	0.25–0.5	0.5	0.5
Clindamycin	0.25–>32	0.25	1
Metronidazole	≤0.06–≤0.06	≤0.06	≤0.06

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TABLE 1 (Continued)

Organism (no. of isolates) and agent	MIC (μg/ml)		
	Range	50%	90%
Parabacteroides distasonis (11)			
Tedizolid	1–2	2	2
Linezolid	2–4	4	4
Ampicillin-sulbactam	4–64	4	32
Piperacillin-tazobactam	4–>64	8	64
Moxifloxacin	0.25–16	0.5	8
Clindamycin	0.25–>32	2	>32
Metronidazole	0.5–1	1	1
Parabacteroides goldsteinii (10)			
Tedizolid	0.5–2	1	2
Linezolid	1–4	4	4
Ampicillin-sulbactam	2–32	8	32
Piperacillin-tazobactam	4–64	8	64
Moxifloxacin	0.25–16	0.5	8
Clindamycin	≤0.06–>32	4	>32
Metronidazole	0.5–1	0.5	1
Parabacteroides merdae (10)			
Tedizolid	0.25–2	1	2
Linezolid	1–4	4	4
Ampicillin-sulbactam	1–64	8	16
Piperacillin-tazobactam	≤0.03–>64	6	64
Moxifloxacin	0.125–8	1.25	8
Clindamycin	≤0.06–>32	0.25	>32
Metronidazole	0.25–2	0.5	1
Fusobacterium necrophorum (10)			
Tedizolid	≤0.06–0.125	≤0.06	≤0.06
Linezolid	0.5–1	0.5	1
Ampicillin-sulbactam	≤0.06–0.125	0.125	0.125
Piperacillin-tazobactam	≤0.03	≤0.03	≤0.03
Moxifloxacin	1–2	1	2
Clindamycin	≤0.06–>64	≤0.06	>64
Metronidazole	0.125–0.5	0.25	0.5
Fusobacterium varium (10)			
Tedizolid	≤0.06–0.25	0.125	0.125
Linezolid	0.25–2	0.5	0.5
Ampicillin-sulbactam	0.5–1	1	1
Piperacillin-tazobactam	1–4	2	4
Moxifloxacin	0.25–>16	4	>16
Clindamycin	0.125–>32	2	>32
Metronidazole	0.25–1	0.5	1
Fusobacterium spp. (10)[a]			
Tedizolid	≤0.06–0.125	≤0.06	≤0.06
Linezolid	0.25–0.5	0.5	0.5
Ampicillin-sulbactam	≤0.06–0.25	≤0.06	≤0.06
Piperacillin-tazobactam	≤0.03–0.06	≤0.03	≤0.03
Moxifloxacin	0.125–2	0.25	2
Clindamycin	≤0.06 = 1	≤0.06	1
Metronidazole	≤0.06 = 0.25	≤0.06	0.125
Porphyromonas spp. (10)[b]			
Tedizolid	≤0.06–1	0.125	0.25
Linezolid	0.5–4	1	2
Ampicillin-sulbactam	≤0.06–2	≤0.06	0.5
Piperacillin-tazobactam	≤0.03–2	≤0.03	≤0.03
Moxifloxacin	0.125–2	0.5	1
Clindamycin	≤0.06–>64	≤0.06	>64
Metronidazole	≤0.06–2	0.125	0.5

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TABLE 1 (Continued)

Organism (no. of isolates) and agent	MIC (μg/ml)		
	Range	50%	90%
Prevotella bivia (10)			
Tedizolid	0.25–4	2	4
Linezolid	2–8	4	4
Ampicillin-sulbactam	0.125–2	1	2
Piperacillin-tazobactam	≤0.03–0.06	≤0.03	≤0.03
Moxifloxacin	0.125–8	4	4
Clindamycin	≤0.06 = >32	≤0.06	>32
Metronidazole	0.25–8	1	8
Prevotella buccae (10)			
Tedizolid	0.5–1	1	1
Linezolid	2–2	2	2
Ampicillin-sulbactam	0.125–1	1	1
Piperacillin-tazobactam	≤0.03	≤0.03	≤0.03
Moxifloxacin	0.5–>16	0.5	>16
Clindamycin	≤0.06–>32	>32	>32
Metronidazole	0.25–0.5	0.5	0.5
Prevotella melaninogenica (10)			
Tedizolid	0.5–1	1	1
Linezolid	2–4	2	4
Ampicillin-sulbactam	0.25–2	1	2
Piperacillin-tazobactam	≤0.03	≤0.03	≤0.03
Moxifloxacin	0.5–>16	1	16
Clindamycin	≤0.06–>64	≤0.03	>64
Metronidazole	0.25–1	0.5	0.5
Prevotella oralis (10)			
Tedizolid	0.125–1	0.25	0.25
Linezolid	0.5–4	2	2
Ampicillin-sulbactam	≤0.06–1	≤0.06	0.5
Piperacillin-tazobactam	≤0.03	≤0.03	≤0.03
Moxifloxacin	0.5–16	1	8
Clindamycin	≤0.06–>32	≤0.06	>32
Metronidazole	≤0.06–1	≤0.06	0.25
Veillonella spp. (10)[c]			
Tedizolid	1–2	2	2
Linezolid	2–8	2	4
Ampicillin-sulbactam	0.125–16	0.5	4
Piperacillin-tazobactam	0.125 = 64	8	64
Moxifloxacin	0.125–8	4	8
Clindamycin	≤0.06–64	≤0.06	4
Metronidazole	0.5–4	2	4
Clostridioides difficile (10)			
Tedizolid	0.25–0.5	0.25	0.25
Linezolid	2–2	2	2
Ampicillin-sulbactam	1–4	2	2
Piperacillin-tazobactam	8–64	8	16
Moxifloxacin	1–16	1	2
Clindamycin	4–16	4	8
Metronidazole	0.25–0.5	0.5	0.5
Clostridium clostridioforme group (10)[d]			
Tedizolid	0.125–0.2	0.25	0.25
Linezolid	2–16	4	16
Ampicillin-sulbactam	0.5–16	1	1
Piperacillin-tazobactam	0.125–>64	4	8
Moxifloxacin	4–16	8	16
Clindamycin	0.25–>32	1	>32
Metronidazole	≤0.06–0.25	≤0.06	0.25
Clostridium innocuum (10)			
Tedizolid	0.5–1	0.5	1
Linezolid	2–>16	4	4

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TABLE 1 (Continued)

Organism (no. of isolates) and agent	MIC (μg/ml)		
	Range	50%	90%
Ampicillin-sulbactam	0.125–0.5	0.25	0.5
Piperacillin-tazobactam	0.5–2	1	2
Moxifloxacin	1–16	2	2
Clindamycin	0.25–>32	0.5	>32
Metronidazole	0.5–0.5	0.5	0.5
Clostridium perfringens (10)			
Tedizolid	0.125–0.25	0.125	0.25
Linezolid	1–16	2	2
Ampicillin-sulbactam	≤0.06–0.5	0.125	0.25
Piperacillin-tazobactam	≤0.03–1	0.25	1
Moxifloxacin	0.25–0.5	0.5	0.5
Clindamycin	≤0.06–>32	0.25	1
Metronidazole	0.25–2	0.5	1
Clostridium ramosum (10)			
Tedizolid	0.5–0.5	0.5	0.5
Linezolid	8–16	8	8
Ampicillin-sulbactam	≤0.06–0.25	0.125	0.125
Piperacillin-tazobactam	0.06–0.5	0.06	0.25
Moxifloxacin	2–>16	2	>16
Clindamycin	0.5–>32	2	4
Metronidazole	0.5–8	1	1
Eggerthella lenta (10)			
Tedizolid	0.25–0.25	0.25	0.25
Linezolid	1–2	1	2
Ampicillin-sulbactam	1–2	1	2
Piperacillin-tazobactam	16–32	16	32
Moxifloxacin	0.125–>16	0.25	4
Clindamycin	≤0.06–32	0.125	16
Metronidazole	0.125–0.25	0.25	0.25
Finegoldia magna (10)			
Tedizolid	0.125–0.25	0.25	0.25
Linezolid	1–2	2	2
Ampicillin-sulbactam	≤0.06–0.25	0.125	0.125
Piperacillin-tazobactam	0.06–0.125	0.06	0.125
Moxifloxacin	0.06–8	0.125	8
Clindamycin	≤0.06–>32	0.25	1
Metronidazole	≤0.06–0.5	0.25	0.5
Parvimonas micra (10)			
Tedizolid	≤0.06	≤0.06	≤0.06
Linezolid	0.5–1	0.5	1
Ampicillin-sulbactam	≤0.06–≥0.06	≤0.06	≤0.06
Piperacillin-tazobactam	≤0.03	≤0.03	≤0.03
Moxifloxacin	0.25–2	0.25	2
Clindamycin	≤0.06–8	≤0.06	0.125
Metronidazole	≤0.06–0.125	0.125	0.125
Peptostreptococcus anaerobius (10)			
Tedizolid	≤0.06–0.125	≤0.06	0.125
Linezolid	0.5–1	0.5	0.5
Ampicillin-sulbactam	0.125–8	0.125	0.25
Piperacillin-tazobactam	0.125–16	0.25	2
Moxifloxacin	0.125–8	0.125	8
Clindamycin	≤0.06–0.5	0.125	0.25
Metronidazole	0.25–1	0.5	0.5

[a]*Fusobacterium nucleatum* (6 isolates), *F. nucleatum* subsp. *animalis* (2), *F. nucleatum* subsp. *funduliforme* (1), and *F. nucleatum* subsp. *vincentii* (1).
[b]*Porphyromonas asaccharolytica* (4 isolates), *Porphyromonas somerae* (3), *Porphyromonas* species (3).
[c]*Veillonella* species (7 isolates), *Veillonella parvula* (3).
[d]*Clostridium aldenense* (4 isolates), *Clostridium bolteae* (3), *Clostridium clostridioforme* (2), and *Clostridium hathewayi* (1).

clinical use of tedizolid for infections with mixed Gram-positive aerobic and anaerobic bacteria, resistant infections with anaerobic bacteria, and/or infections in patients with multiple drug allergies.

The marrow toxicity of longer-duration oxazolidinone therapy has been of clinical concern; however, a recent retrospective study of patients who received tedizolid for a median duration of 28 days (interquartile range, 14 to 59 days), including patients with prosthetic joint infections and osteomyelitis, found it to be well tolerated and showed only an 8.7% discontinuation rate (22).

Tedizolid has good and underappreciated *in vitro* activity against a wide variety of anaerobes, including those typically isolated from ABSSSIs, such as diabetic foot infections. Clinicians might consider its use as a potential therapeutic partner in mixed infections where *S. aureus* and anaerobes are involved.

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