In vitro activity of tedizolid and comparator agents against Gram-positive pathogens responsible for bone and joint infections

Pauline Ract,1,2 Caroline Piau-Couapel,3 Fabrice Compain,2 Michel Auzou,1 Jocelyn Michon4 and Vincent Cattoir3,5,*

Abstract

Tedizolid, a second-generation oxazolidinone that displays a potent activity against Gram-positive pathogens, could be an interesting option for the treatment of bone and joint infections (BJIs). The aim of the study was to determine minimal inhibitory concentration (MIC) of tedizolid against a collection of 359 clinical isolates involved in clinically-documented BJIs and to compare them to those of comparator agents used in Gram-positive infections. Of the 104 Staphylococcus aureus and 102 coagulase-negative staphylococci (CoNS) isolates, 99 and 92% were categorized as susceptible to tedizolid, respectively (MIC90=0.25/0.5 µg ml⁻¹ and MIC90=0.25/0.5 µg ml⁻¹), regardless of their methicillin resistance. MIC50 and MIC90 for the 51 enterococci, the 50 Corynebacterium spp. and the 52 Propionibacterium spp. were either equal or inferior to 0.5 µg ml⁻¹. Altogether, tedizolid possessed a potent in vitro activity against most of the BJI Gram-positive pathogens with 95% of them exhibiting a MIC ≤0.5 µg ml⁻¹.

Bone and joint infections (BJIs) cause serious morbidity and mortality since they are difficult to manage, often requiring prolonged antimicrobial therapy and surgical intervention [1]. They range from septic arthritis, to osteomyelitis, to prosthetic joint infections (PJs) [2]. Notably, PJs have become an important medical burden with great clinical and economic impact, especially in the elderly [2, 3]. Gram-positive bacteria are responsible for the majority of BJIs, with Staphylococcus aureus being the most common bacteria involved in septic arthritis and osteomyelitis. Besides S. aureus, coagulase-negative staphylococci (CoNS) are also commonly recovered in PJs, followed by streptococci, enterococci, corynebacteria and Propionibacterium acnes [3]. The selection of the most appropriate systemic antibiotic for BJI therapy is challenging and must take into consideration numerous parameters such as pathogen(s), antimicrobial susceptibility profile(s), pharmacokinetics criteria (especially penetration into bone), presence of pretherapeutic material and tolerance to the drug(s) [1]. Currently, one of the most important issues is the increasing importance of multidrug resistance worldwide, particularly in staphylococci and enterococci for which therapeutic options are limited [4].

Tedizolid (formerly known as TR-700 or torezolid) is a novel once-daily dosed antibiotic that was recently approved by the FDA for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) [5]. Like linezolid, it belongs to the oxazolidinone class and exhibits its bacteriostatic effect through the inhibition of bacterial protein synthesis by binding to the 23S rRNA of the 50S subunit of the ribosome [6]. It displays activity against a broad range of Gram-positive bacteria such as staphylococci, streptococci and enterococci, including multidrug-resistant isolates [5, 6]. As compared to linezolid, tedizolid is generally 4- to 32-fold more potent in vitro while it retains activity against linezolid-resistant cfr-bearing strains [7–9]. Note that ribosomal mutations and plasmid-mediated OprrA confer resistance to both linezolid and tedizolid [7, 8]. Very interestingly, tedizolid seems to display a lower potential for myelotoxicity and neurotoxicity than linezolid [10], which could be of value when considering prolonged treatment durations as previously reported [11, 12].

Although tedizolid is not indicated in the treatment of BJIs, it is a promising candidate in this context. Indeed, its in vivo efficacy has been demonstrated in experimental foreign-body-associated osteomyelitis due to S. aureus or Staphylococcus epidermidis [13].

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Author affiliations: 1CHU de Caen, Service de Microbiologie, Caen, France; 2CHU de Rennes, Service de Bactériologie-Hygïène Hospitalière, Rennes, France; 3CHU de Caen, Service de Maladies Infectieuses et Tropicales, Caen, France; 4CNR de la Résistance aux Antibiotiques (laboratoire associé “Entérocoques”), Rennes, France.

*Correspondence: Vincent Cattoir, vincent.cattoir@chu-rennes.fr

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Abbreviations: BJI, bone and joint infection; CoNS, coagulase-negative staphylococci; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimal inhibitory concentration; PJI, prosthetic joint infection.
**Staphylococcus epidermidis** [13, 14]. In addition, tedizolid has been successfully used in a case report of a PJI caused by vancomycin-resistant enterococci [15] and it is currently under a phase II evaluation as an oral prolonged (4–12 weeks) treatment for BJIs in adult patients (clinical trial no. NCT009045 on clinicaltrials.gov/). However, very few studies have evaluated the *in vitro* activity of this novel drug against staphylococci involved in PJIs and tedizolid has never been tested against the main Gram-positive bacterial species found in BJIs other than staphylococci, such as *Enterococcus* spp., *Corynebacterium* spp. and *Propionibacterium* spp. [16, 17].

The aim of the study was then to determine the *in vitro* activity of tedizolid against a large collection of clinical isolates recovered from clinically-documented BJIs and to compare it to that of comparator agents (including linezolid) classically used in the treatment of Gram-positive infections.

A total of 359 non-redundant bacterial BJI isolates, collected from 2013 to 2016 at the University Hospital of Caen (France), were included in this study: 104 *S. aureus*, 102 CoNS, 51 *Enterococcus* spp., 50 *Corynebacterium* spp. and 52 *Propionibacterium* spp. All BJIs (including osteomyelitis, septic arthritis and prosthetic joint infections) were assessed by an infectious disease specialist according to national and international guidelines [18, 19]. Clinical isolates were recovered from various surgical samples, including bone biopsies and articular fluids. All strains were unambiguously identified to the species level using matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (Microflex; Bruker-Daltonics, Bremen, Germany).

Minimum inhibitory concentrations (MICs) of tedizolid, linezolid, vancomycin, teicoplanin, daptomycin, ceftaroline and cefotibiprole were determined in duplicate by the broth microdilution reference method using cation-adjusted Mueller-Hinton broth (CA-MHB) (Becton-Dickinson, Le Pont de Claix, France), in accordance with European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (http://www.eucast.org/). For daptomycin, the test medium was supplemented with 50 µg ml$^{-1}$ of calcium. For *Corynebacterium* spp. and *P. acnes*, the CA-MHB was supplemented with 5% of horse blood. The antibiotics were tested in serial twofold dilutions, with concentrations ranging from 0.03 to 8 µg ml$^{-1}$. The MIC was defined as the lowest concentration
of antimicrobial agent that inhibited the growth at 35 ±2 °C after 24 h of incubation in aerobic conditions (for staphylococci, enterococci and Corynebacterium spp.) or after 48 h in anaerobic conditions (for P. acnes). S. aureus ATCC 29213, E. faecalis ATCC 29212, Streptococcus pneumoniae ATCC 49619 were used as quality control.
strains. MICs were interpreted according to 2017 EUCAST clinical breakpoints (http://www.eucast.org/).

Among the 104 S. aureus isolates, 77 (74 %) and 27 (26 %) were susceptible and resistant to methicillin, respectively. All but one (99 %) isolate were categorized as susceptible to tedizolid (MIC$_{50}$=0.12 µg ml$^{-1}$; MIC$_{90}$=0.25 µg ml$^{-1}$) according to the EUCAST clinical breakpoint (susceptible if MIC $\leq$0.5 µg ml$^{-1}$), regardless of the methicillin resistance (Table 1, Fig. 1). Even though 100 % of isolates were susceptible to linezolid, MIC$_{50}$ and MIC$_{90}$ values were both 8-fold higher than those observed for tedizolid (Table 1). The unique non-susceptible strain exhibited a MIC of tedizolid at 1 µg ml$^{-1}$ while the MIC of linezolid was at 4 µg ml$^{-1}$. Regarding the other molecules tested, 100, 100, 95, 100 and 100 % of the strains were categorized as susceptible to vancomycin, teicoplanin, daptomycin, ceftaroline and ceftobiprole, respectively (Table 1).

Of the 102 CoNS isolates, 63 (62 %) and 39 (38 %) were susceptible and resistant to methicillin, respectively. The three most frequently isolated species were: S. epidermidis (56 %), S. capitis (22 %) and S. lugdunensis (11 %). Although tedizolid was 4- to 8-fold more active in vitro than linezolid (MIC$_{50}$/MIC$_{90}$=0.25/0.5 versus 2/2 µg ml$^{-1}$, respectively), 92 and 100 % of CoNS isolates were susceptible to tedizolid and linezolid, respectively (Table 1). There was no difference between MSCoNS and MRCoNS groups (Fig. 1). Among these 8 tedizolid-non-susceptible strains, 7 exhibited a MIC of tedizolid at 1 µg ml$^{-1}$ and another at 2 µg ml$^{-1}$ while MICs of linezolid varied from 1 to 4 µg ml$^{-1}$. Concerning comparative antimicrobial agents, 100, 98 and 86 % of CoNS isolates were susceptible to vancomycin, teicoplanin and daptomycin, respectively (Table 1). Applying EUCAST susceptible breakpoints for S. aureus, both cetaroline and ceftobiprole inhibited all CoNS isolates at $\leq$1 and $\leq$2 µg ml$^{-1}$, respectively (Table 1). The main CoNS species involved in BJIs (i.e. S. epidermidis, S. capitis and S. lugdunensis) showed similar susceptibility patterns to tedizolid (data not shown). By comparing the two groups of staphylococci, CoNS seemed to be slightly less susceptible to tedizolid than S. aureus isolates, with MIC$_{50}$ and MIC$_{90}$ 2-fold more elevated (Table 1).

Amongst the 51 enterococcal strains, E. faecalis (n=39; 76 %) was the main species followed by E. faecium (n=10; 20 %), E. avium (n=1; 2 %) and E. casseliflavus (n=1; 2 %). Tedizolid was also more active than linezolid (100 % of susceptible strains) with MIC$_{50}$ and MIC$_{90}$ 4-fold lower (MIC$_{50}$/MIC$_{90}$=0.5/0.5 versus 2/2 µg ml$^{-1}$, respectively) (Table 1). Note that only four strains exhibited a MIC higher than 0.5 µg ml$^{-1}$ (susceptibility breakpoint for staphylococci) and there was no significant difference of tedizolid susceptibility between E. faecalis and E. faecium (Fig. 1). Finally, 100 % of enterococci were susceptible to both vancomycin and teicoplanin (Table 1).

Fifty strains of Corynebacterium spp. were studied, including 20 C. striatum (40 %), 8 C. amycolatum (16 %) and 5 C. jeikeium (10 %). Tedizolid and linezolid were similarly active against corynebacteria with MIC$_{50}$ and MIC$_{90}$ at 0.5/0.5 and 0.5/1 µg ml$^{-1}$, respectively (Table 1). Interestingly, there was no significant difference in terms of tedizolid MICs between penicillin-susceptible and -resistant isolates (Fig. 1). Four strains exhibited a tedizolid MIC higher than 0.5 µg ml$^{-1}$: 3 strains (1 C. amycolatum, 1 C. aurimucosum and 1 Corynebacterium sp.) with a MIC at 1 µg ml$^{-1}$ and 1 strain of C. simulans with a MIC at 4 µg ml$^{-1}$. Finally, 100 % of tested strains were categorized as susceptible to linezolid and vancomycin (Table 1).

The vast majority of clinical isolates of Propionibacterium spp. belonged to the species P. acnes (46/52; 88 %). Tedizolid was highly active against these microorganisms (MIC$_{50}$=0.12 µg ml$^{-1}$, MIC$_{90}$=0.5 µg ml$^{-1}$) and no isolates had a MIC $>$0.5 µg ml$^{-1}$ (Table 1). By comparison, MIC$_{50}$ and MIC$_{90}$ of linezolid were 2- to 4-fold higher (MIC$_{50}$=0.5 µg ml$^{-1}$, MIC$_{90}$=1 µg ml$^{-1}$) (Table 1). MICs of all other antibiotics were also low and 100 % of the strains were susceptible to vancomycin (Table 1).

These results demonstrate that tedizolid has a potent activity against most of the 359 Gram-positive pathogens associated with BJIs studied here, with 342 of them (95 %) exhibiting a MIC inferior or equal to 0.5 µg ml$^{-1}$ (EUCAST susceptibility breakpoint for staphylococci). Interestingly, its in vitro activity was 4- to 8-fold greater than enterococci and staphylococci than that of the currently used oxazolidine linezolid (irrespective of β-lactam resistance). These data are consistent with previous data on non-BJI isolates that have reported MIC$_{50}$ and MIC$_{90}$ values for tedizolid of 0.12–0.25 and 0.25–0.5 µg ml$^{-1}$ for staphylococci and of 0.25–0.5 and 0.5–1 µg ml$^{-1}$ for enterococci, respectively [5, 6, 8, 9]. When compared with the only two studies specifically evaluating in vitro activity against PJI staphylococcal isolates, results obtained are also similar [16, 17]. In the first study, MIC$_{50}$ and MIC$_{90}$ of tedizolid were 0.5 and 0.5 µg ml$^{-1}$ for S. aureus (n=97) and 0.25 and 0.5 µg ml$^{-1}$ for S. epidermidis (n=74), respectively [16]. In the second study, MIC$_{50}$ and MIC$_{90}$ of tedizolid were 0.19 and 0.38 µg ml$^{-1}$ for S. epidermidis (n=183), respectively [17]. Nine strains (1 S. aureus and 8 CoNS with MICs of 1–2 µg ml$^{-1}$) were categorized as non-susceptible to tedizolid in the present study. All these patients had received multiple broad-spectrum antibiotics before sampling, but no oxazolidinones were part of their therapeutic regimens. These nine strains were isolated from different patients and were distributed equally over the three-year period of this study, which does not suggest any increase in tedizolid resistance rates.

Even though no interpretive clinical breakpoints have been yet defined for tedizolid and organisms other than staphylococci, all isolates of Enterococcus spp., Corynebacterium spp. and Propionibacterium spp. tested here showed MIC$_{50}$ values $\leq$0.5 µg ml$^{-1}$. These concentrations are easily reached in vivo at the recommended 200 mg once-daily dose [20], suggesting that tedizolid could be an interesting therapeutic option for BJI involving these pathogens.
Moreover, pharmacokinetics studies showed satisfying bone diffusion for tedizolid [21].

To the best of our knowledge, no study evaluating in vitro activity of tedizolid against *Corynebacterium* spp. and *Propionibacterium* spp. has been conducted so far. Nonetheless, MIC50 and MIC90 values determined here for these genera are similar to those obtained for staphylococci and enterococci [5, 6, 8, 9]. This demonstrates that tedizolid exerts a potent and similar in vitro activity against the different Gram-positive bacterial pathogens. This discrepancy of categorization between linezolid and tedizolid is likely due to the difference of susceptibility breakpoints (≤0.5 mg l⁻¹ for tedizolid and ≤4 mg l⁻¹ for linezolid), which depend on epidemiologic cutoff values (ECCOF) and pharmacokinetic-pharmacodynamic (PK-PD) parameters.

Most isolates collected in this study were susceptible to all tested antibiotics while no linezolid resistance was observed in the study. This is a limit of the study as well as its monocentric design. These results should then be extrapolated with caution to other epidemiological contexts, especially in regions displaying higher proportions of multidrug-resistant Gram-positive bacteria.

In conclusion, results of this study demonstrate that tedizolid has an excellent in vitro activity against Gram-positive pathogens associated with BJIs. Also, this is the first study evaluating the in vitro activity of tedizolid against uncommon Gram-positive pathogens such *Corynebacterium* and *Propionibacterium* species. Note that currently there are no EUCAST clinical breakpoints of tedizolid for non-staphylococcal isolates but the data presented here and elsewhere suggest that a breakpoint similar to that for staphylococci may be appropriate for other Gram-positives. In the light of its potent in vitro activity and adverse effects generally observed with other anti-Gram positive antibiotic options (such as glycopeptides, daptomycin or linezolid), tedizolid appears to be a promising option and future clinical studies should confirm its place in the arsenal for the treatment of BJIs.

References


