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REVIEW

Potential role of tedizolid phosphate in the treatment of acute bacterial skin infections

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Abstract: Tedizolid phosphate (TR-701), a prodrug of tedizolid (TR-700), is a next-generation oxazolidinone that has shown favorable results in the treatment of acute bacterial skin and skin-structure infections in its first Phase III clinical trial. Tedizolid has high bioavailability, penetration, and tissue distribution when administered orally or intravenously. The activity of tedizolid was greater than linezolid against strains of *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. in vitro studies, including strains resistant to linezolid and those not susceptible to vancomycin or daptomycin. Its pharmacokinetic characteristics allow for a once-daily administration that leads to a more predictable efficacy and safety profile than those of linezolid. No hematological adverse effects have been reported associated with tedizolid when used at the therapeutic dose of 200 mg in Phase I, II, or III clinical trials of up to 3 weeks of tedizolid administration. Given that the clinical and microbiological efficacy are similar for the 200, 300, and 400 mg doses, the lowest effective dose of 200 mg once daily for 6 days was selected for Phase III studies in acute bacterial skin and skin-structure infections, providing a safe dosing regimen with low potential for development of myelosuppression. Unlike linezolid, tedizolid does not inhibit monoamine oxidase in vivo, therefore interactions with adrenergic, dopaminergic, and serotonergic drugs are not to be expected. In conclusion, tedizolid is a novel antibiotic with potent activity against Gram-positive microorganisms responsible for skin and soft tissue infections, including strains resistant to vancomycin, linezolid, and daptomycin, thus answers a growing therapeutic need.

Keywords: oxazolidinone, TR-700, TR-701 FA, tedizolid, skin and soft tissue infections, linezolid resistance

Introduction

Skin and soft tissue infections are one of the main reasons people seek health care and account for approximately 7%–10% of US hospital admissions.[1,2] During the 2000–2004 period there was a 28.9% increase in the number of hospitalizations due to skin and soft tissue infections.[3] A study conducted in Taiwan reported that approximately 7.7% of hospitalized patients presented with at least one skin and soft tissue infection during the 2005–2007 period.[4]

Despite the fact that the etiology can be variable, *Staphylococcus aureus* is the microorganism most often involved.[5] In recent years, an increase has been observed in the number of methicillin-resistant *S. aureus* (MRSA) strains, which makes the management of these infections more difficult. Thus, the rate of methicillin resistance in *S. aureus* strains from skin and soft tissue infections ranges from 22.8% in Europe to 35.9% in North America.[5]

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Previously, infections due to MRSA strains were limited to the hospital setting. However, in the last decade, there has been an emergence of community-associated MRSA strains. For instance, a 59% prevalence of MRSA strains has been reported (range: 15%–74%) in patients with skin and soft tissue infections who were admitted to emergency wards in eleven US cities.[6] The USA 300 strain was identified in 97% of MRSA strains. Its high capacity for diffusion means that the USA 300 strain is now considered to be epidemic in the USA and is becoming significant in other parts of the world.[7] Moreover, a decrease in this strain's sensitivity to several antibiotics has been observed, which could make the success of antibiotic treatment even more difficult.[7] New clones of community MRSA have been reported to be on the rise in other European countries.[8,9]

Currently, the emergence of community-associated and hospital-origin MRSA strains from patients with skin and soft tissue infections seems to be under control.[10] According to a recent study, the rate of skin and soft tissue infections due to community MRSA ranged from 76.8 (75.0–78.6) per 100,000 people/year in 2005 to 64.0 (62.4–65.6) per 100,000 people/year in 2010 (P = 0.62).[10] Thus, 60% of skin and soft tissue infections were caused by MRSA strains in 2005, with an increase of up to 62% in 2006 and a significant annual reduction reaching 52% in 2010. In addition, the rate of hospital MRSA infections decreased from 0.7 (0.5–0.8) per 100,000 people/year in 2005 to 0.4 (0.2–0.5) per 100,000 people/year in 2010 (P = 0.02). No trend was observed in the percentage of infections due to MRSA strains when the origin of the infections was the hospital (P = 0.96).

Vancomycin is the antibiotic that has been used most often to treat infections due to MRSA strains. However, its efficacy has been compromised by the emergence of *S. aureus* strains with heteroresistance to glycopeptide (heterogeneous vancomycin-intermediate *S. aureus* [hVISA] strains), intermediate resistance (vancomycin-intermediate *S. aureus* [VISA] strains) and, occasionally, complete resistance (vancomycin-resistant *S. aureus* strains).[11–14]

Linezolid was the first representative member of the oxazolidinone family introduced into the pharmaceutical market. Although it continues to show excellent activity, in recent years, MRSA strains have been isolated that are resistant to this antibiotic (minimum inhibitory concentration [MIC] >8 mcg/mL) due to the mutations in 23S ribosomal (r) RNA (namely G2576T) or ribosomal protein L3 or by the presence of the *cfr* gene.[15,16] The presence of the *cfr* gene confers additional resistance to a high number of protein synthesis inhibitors (phenicols, lincosamides, streptogramins, pleuromutilins, oxazolidinones, and 16-membered macrolides)[17–19] and it has the capacity for horizontal transfer via mobile genetic elements.[20,21]

Other antibiotics have been incorporated into the available therapeutic arsenal to compensate for the emergence of resistant strains, although we consider their use is not without limitations.

A close correlation has been described between the reduction in sensitivity to daptomycin and resistance to vancomycin in VISA and hVISA strains.[22,23] This finding irequires precaution when considering daptomycin as a therapeutic alternative in infection due to VISA or hVISA strains. In terms of its safety profile, several severe cases of daptomycin-induced eosinophilic pneumonia[24] have been described and treatment requires monitoring for possible muscular toxicity associated with the antibiotic. In particular, patients with impaired renal function or on concomitant treatment with statins should be monitored more closely.[25]

As a result of these issues and given the limited number of therapeutic options available for these infections, new therapeutic alternatives are being and have been developed for the treatment of skin and soft tissue infections, especially those produced by resistant Gram-positive microorganisms. One such new development is tedizolid (TR-700), which belongs to the family of oxazolidinones and is the active moiety of tedizolid phosphate (TR-701). One of its greatest advantages is that its activity is greater than that of vancomycin and linezolid against microorganisms involved mainly in skin and soft tissue infections, including strains of *S. aureus* that carry the *cfr* gene, which, as mentioned, confers resistance to linezolid.[20,26] Another of its advantages, which it shares with linezolid, is its availability both for parenteral and oral administration, allowing for outpatient treatment.

This review will describe the role of tedizolid phosphate (TR-701) in the treatment of skin and soft tissue infections.

Pharmacology

Tedizolid (TR-700 or DA-7157; formerly torezolid) is a next-generation oxazolidinone whose chemical differences compared with first-generation oxazolidinones grant it greater potency, a better spectrum of activity, and a lower resistance profile.

In addition to other advantages that will be listed further on in this paper, the prodrug tedizolid phosphate (TR-701 or DA-7218 or DA-7158; formerly torezolid phosphate) shares with linezolid the ability to be administered orally and intravenously; good bioavailability, tissue penetration, and distribution; and good activity against MRSA.[27]

Tedizolid phosphate is a basic compound with a molecular weight of 494.28 and chemical structure (R)-[3-(4-(2-(2-methyl tetrazole-5-yl)pyridin-5-yl)-3-fluorophenyl)-2-oxo-5-oxazolidinyl] methyl disodium phosphate, which is hydrolyzed by phosphatases to the active moiety tedizolid (R)-3-(4-(2-(2-methyl tetrazole-5 yl)pyridin-5-yl)-3 fluorophenyl)-5-hydroxy methyl oxazolidine-2-one.[28]

Mechanism of action

In a similar fashion to linezolid, tedizolid inhibits the synthesis of bacterial proteins by binding to the 50S subunit of the ribosome and preventing the formation of the "70S complex" formed by the binding of N-formylmethionine-tRNA, the 50S subunit, and the 70S subunit. In this way, it prevents the translation process in the first step of protein synthesis.[29,30]

Pharmacokinetics

Absorption, distribution, metabolism, and excretion

A study evaluated the pharmacokinetics in a murine model of tedizolid phosphate administered intravenously at doses of 5, 10 and 20 mg/kg and orally at doses of 20, 50, and 100 mg/kg, and of tedizolid 10 mg/kg administered both intravenously and orally.[28] Dose-proportional pharmacokinetics were observed for all the doses evaluated. The oral administration of tedizolid phosphate resulted in rapid gastrointestinal absorption, with tedizolid detected in plasma within 15 minutes (time to maximum concentration [T_{max}]: 25.5–65.0 minutes). Plasma area-under-the-curve (AUC) values for tedizolid were proportional to the doses of tedizolid phosphate administered. Similarly, the formation of tedizolid from tedizolid phosphate intravenous (IV) was rapid: it was detected in plasma at the first blood sampling time (1 minute) and rapidly reached T_{max} (7.85–12.1 minutes) for the three doses studied. The AUC values for tedizolid detected in blood were proportional to the IV doses of tedizolid phosphate. Both tedizolid phosphate (oral and IV) and tedizolid were practically undetectable in urine after 24 hours and in the gastrointestinal tract of the animals, including feces. Another study analyzed the pharmacokinetics of tedizolid phosphate after the administration of a dose of 10 mg/kg in rats administered by both oral and IV routes.[31] Table 1 shows the pharmacokinetic parameters of tedizolid phosphate and tedizolid after the administration of tedizolid phosphate to rats corresponding to these two studies.[28,31]

The pharmacokinetics of tedizolid phosphate in other species, such as rats and dogs has also been investigated.[32] As in the two studies already discussed, tedizolid phosphate administered orally and intravenously was rapidly transformed into tedizolid both in vivo and in vitro in all the species analyzed.

In healthy humans, a bioavailability of 91.47% has been estimated after the oral administration of a dose of 200 mg of tedizolid phosphate.[33] Although one study found an increase in the T_{max} value and reduction in the maximum concentration (C_{max}) value of tedizolid after 10 hours of fasting, the AUC value was similar both with fasting and when administered with food. Thus, since AUC is the most important predictor

Table 1 Pharmacokinetic parameters of tedizolid phosphate and tedizolid after the administration of tedizolid phosphate to rats[28,31]

Tedizolid phosphate IV					**Tedizolid phosphate OR**			
Dose (mg/kg)	5 mg/kg (n = 7)[28]	10 mg/kg (n = 7)[28]	20 mg/kg (n = 9)[28]	10 mg/kg[31]	20 mg/kg (n = 10)[28]	50 mg/kg (n = 8)[28]	100 mg/kg (n = 9)[28]	10 mg/kg[31]
AUC (mcg * min/mL)	313 ± 75.4	44.7 ± 16.9	86.3 ± 27.9	3.216	44.7 ± 16.9	86.3 ± 27.9	163 ± 40.0	2.988
$T_{½}$ (min)	13.8 ± 3.64	133 ± 30.8	159 ± 32.1	205.2	133 ± 30.8	159 ± 32.1	162 ± 29.6	229.2
C_{max} (mcg/mL)	–	–	–	8.81	0.214 ± 0.0833	0.320 ± 0.102	0.440 ± 0.0995	8.37
T_{max} (min)	–	–	–	–	45.0 ± 24.5	80.6 ± 26.5	130 ± 73.5	30
Cl (mL/min/kg)	16.0 ± 3.40	45.0 ± 24.5	80.6 ± 26.5	3.11	–	–	–	–
Vd_{ss} (mL/kg)	84.7 ± 14.2	0.214 ± 0.0833	0.320 ± 0.102	0.918	–	–	–	–
F (%)	–	–	–	–	3.44	2.66	2.51	92.8
Tedizolid IV					**Tedizolid OR**			
AUC (mcg * min/mL)	905 ± 105	1.780 ± 334	4.070 ± 1.140		2.890 ± 857	8.580 ± 3.230	17.500 ± 6.710	
$T_{½}$ (min)	106 ± 12.0	112 + 19.2	115 ± 29.8		158 ± 24.5	276 ± 113	366 ± 85.7	
C_{max} (mcg/mL)	12.5 ± 1.16	20.8 ± 3.41	45.4 ± 8.95		14.0 ± 4.43	22.9 ± 8.13	34.6 ± 10.1	
T_{max} (min)	12.1 ± 4.88	7.85 ± 4.88	10.6 ± 12.6		25.5 ± 14.2	43.1 ± 24.6	65.0 ± 72.3	

Abbreviations: AUC, area under the curve; Cl, total body clearance; C_{max}, maximum concentration; F, absolute oral bioavailability; IV, intravenous; OR, oral; $T_{½}$, half-life; T_{max}, time to maximum concentration; Vd_{ss}, volume of distribution at steady state.

of efficacy,[34] there are no dietary restrictions for taking the drug.[35]

Similar to the animal models,[32] tedizolid phosphate administered orally or intravenously is rapidly transformed into tedizolid through hydrolysis of the phosphate group by phosphatases.[27] In addition, tedizolid was the major moiety detected (94.54%–98.23% of radioactivity administered) in plasma in a study that evaluated the oral administration of a single dose of radioactively labeled tedizolid phosphate in healthy adults.[36]

Two studies have evaluated the pharmacokinetics of tedizolid after the administration of multiple doses of tedizolid phosphate in healthy adults (Table 2).[33,37] In one of them linezolid was used as a comparator treatment.[37]

The pharmacokinetic parameters of tedizolid have been determined in other studies in which increasing single doses of tedizolid phosphate were administered, both orally (200–1200 mg)[38] and intravenously (100–400 mg).[33] Less variability was observed in the systemic exposure of tedizolid when it was compared with linezolid.[37] Thus, the pharmacokinetic parameters of tedizolid corresponding to day 1 were predictive of those observed at steady state.[33,37] As in the animal models, the AUC and C_{max} values of tedizolid showed linear pharmacokinetics almost proportional to the tedizolid phosphate dose, both in the studies with multiple doses and with single doses.[37,38]

Two studies have evaluated a model that reflects the superior pharmacokinetics of tedizolid phosphate.[39,40] In a Phase II dose-ranging study of efficacy and tolerability of 200, 300, and 400 mg of tedizolid phosphate in the treatment of complicated skin and skin-structure infections, clinical cure and microbiological eradication rates were above 90% with all three doses.[40] Population pharmacokinetics favored a two-compartment model over one disposition compartment. In the other Phase II study, nonlinear mixed effects modeling was performed to analyze pharmacokinetics of tedizolid phosphate in patients with acute bacterial skin and skin-structure infections (ABSSSI).[39] Results showed that the pharmacokinetics was well described by a two-compartment model with zero-order dose delivery to the depot compartment and subsequent first-order absorption.

Plasma protein binding in healthy adults has been estimated between 86.1% and 91.9%, with a mean of 89.44% ± 1.58%.[41]

The volume of distribution of tedizolid has been reported to be between two and three times higher than the value observed with linezolid.[37] Further, in a study with healthy adults, it was observed that the levels of free tedizolid in muscle and adipose tissue were similar to those observed

Table 2 Pharmacokinetic parameters of tedizolid after the administration of multiple doses of tedizolid phosphate to healthy adults[33,37]

Dose of tedizolid phosphate	TR-701 200 mg QD OR[37]		TR-701 300 mg QD OR[37]		TR-701 400 mg QD OR[37]		TR-701 200 mg QD IV[33]		Linezolid 600 mg BID[37]	
Parameter	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 7**	**Day 1**	**Day 15**
C_{max} (mcg/mL)	1.8 (1.2)	1.8 (0.4)	2.1 (0.5)	2.5 (0.4)	4.2 (0.8)	4.5 (0.9)	2.34 (0.64)	3.01 (0.66)	12.2 (3.0)	14.6 (4.6)
C_{min} (mcg/mL)	0.3 (0.1)	0.4 (0.2)	0.4 (0.1)	0.5 (0.2)	0.7 (0.2)	0.8 (0.2)	–	–	1.7 (1.4)	4.9 (3.3)
T_{max} (hr) (range)	3.0 (1.5–4.0)	3.0 (2.0–4.0)	2.0 (1.5–4.0)	1.8 (1.5–4.0)	4.0 (1.0–4.0)	3.0 (2.0–8.0)	1.08 (0.92–1.50)	1.17 (0.92–1.50)	1.0 (0.4–1.5)	1.5 (1.0–4.0)
$T_{½}$ (hr)	11.1 (1.2)	10.2 (2.0)	10.1 (1.4)	9.4 (1.2)	8.0 (1.2)	8.4 (1.0)	9.33 (1.5)	12.4 (1.25)	3.8 (1.7)	4.7 (1.3)
AUC (mcg * hr/mL)	21.6 (6.5)	22.5 (6.5)	29.6 (7.5)	30.7 (6.1)	54.0 (8.2)	53.2 (7.9)	22.29 (4.24)	29.19 (6.22)	78.1 (31.6)	108.9 (42.7)
Accumulation ratio	1.04		1.04		0.99		–	–	1.39	
Cl/F (L/hr)	10.0 (2.8)	9.5 (2.7)	10.6 (2.4)	10.1 (1.8)	7.6 (1.1)	7.7 (1.1)	6.37 (1.19)	5.87 (1.41)	8.7 (3.1)	6.4 (2.7)
V/F (L)	155 (29)	143 (51)	155 (37)	136 (23)	86 (13)	92 (18)	77.6 (15.9)	80.1 (21.0)	43 (11)	43 (11)

Abbreviations: AUC, area under the curve; BID, twice daily; Cl/F (L/hr), apparent oral clearance; C_{max}, maximum concentration; C_{min}, minimum concentration; IV, intravenous; OR, oral; QD, daily; $T_{½}$, half-life; T_{max}, time to maximum concentration; V/F (L), apparent volume of distribution.

in plasma after the oral administration of a single dose of 600 mg of tedizolid phosphate.[42] Ratio of unbound AUC in tissues over unbound (free) AUC in plasma (fAUC tissue/fAUC plasma) of tedizolid was 1.1 ± 0.2 in adipose tissue and 1.2 ± 0.2 in muscle tissue. These values, together with the rest of the pharmacokinetic parameters, support the administration of tedizolid phosphate in a single daily dose.[33,37,38] Moreover, only modest accumulation of ~30% tedizolid was observed in the studies that evaluated the administration of multiple doses of tedizolid phosphate, which would justify its safety profile.[33,43]

Tedizolid is mostly eliminated in the feces; the urine is a minor elimination route. Two studies in healthy adults showed that less than 1% of the tedizolid phosphate dose administered was eliminated in urine unchanged or as tedizolid.[37,38] Similarly, in a study in which a single dose of radioactively labeled tedizolid phosphate was administered to healthy adults, only 18% of the radioactive dose was recovered from the urine, whereas 81.5% was recovered from the feces.[36] In both cases, the greatest metabolite was the sulfate analog, 10% or which was present in the urine and 69% in the feces.[36] N-demethylation and oxidation were minor elimination routes.

Three-stage hierarchical population pharmacokinetic modeling yielded the following estimations: geometric mean clearance of 8.28 L/hour (between-patient variability, 32.3%), a volume of the central compartment of 71.4 L (24.0%), and a volume of the peripheral compartment of 27.9L (liters) (35.7%) in patients with skin and soft tissue infections.[40]

Special populations

As mentioned, tedizolid phosphate is eliminated via the urine to a lesser extent and its pharmacokinetics is unchanged in subjects with severe renal impairment. Therefore, it is not necessary to adjust this drug in patients with reduced renal function.[44] Likewise, the pharmacokinetics of tedizolid phosphate was not significantly altered in subjects with moderate to severe hepatic impairment,[45] so dose adjustments should not be necessary in this patient population either.

In a recently completed Phase I clinical trial that compared tedizolid pharmacokinetics following oral administration of 200 mg tedizolid phosphate in young patients (18–45 years) with elderly patients (>65 years), no changes were observed.[46] In another study, the pharmacokinetic profile of a single oral or IV administration of 200 mg tedizolid phosphate to healthy adolescents (12–17 years) was similar to that observed in adults.[47]

Pharmacodynamics

The pharmacodynamic characteristics of tedizolid phosphate were evaluated in a study comparing the efficacy of the dose fractionation of tedizolid phosphate in a neutropenic mouse-thigh model of methicillin-sensitive *S. aureus* (MSSA) and MRSA infections.[34] The total tedizolid phosphate doses were provided as doses equivalent to tedizolid. The $AUC/MIC_{0–24\ h}$, $T > MIC_{0–24\ h}$, and $C_{max}/MIC_{0–24\ h}$ ratios of free drug were calculated for daily doses of tedizolid phosphate of 10, 20, 36, and 72 mg/kg/24 hours, fractionated into one, two, or four times daily. According to the results, the $AUC/MIC_{0–24\ h}$ pharmacodynamic ratio obtained the best correlation with the efficacy of tedizolid (r^2:0.984). The value of this ratio was 45 (22.5/0.5) for a tedizolid phosphate regimen of 200 mg daily on day 15 of treatment in healthy volunteers, which was higher than the value observed with linezolid (108.9/4:27.3).[37]

Spectrum of activity

In general, tedizolid shows excellent activity against aerobic Gram-positive microorganisms, including linezolid-resistant strains. In contrast, its use in Gram-negative infections is limited, given the high MIC of the antibiotic against these microorganisms.

Although the clinical breakpoints for tedizolid have not yet been defined, the objective of one study was to provide some conservative disc diffusion and MIC cut-off values for tedizolid (Table 3).[48] In general, an MIC of ≤2 mcg/mL was used as the cut-off point of sensitivity.

Aerobic Gram-positive microorganisms

The activity of tedizolid in vitro has been found to be greater than that of linezolid against strains of *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp., including strains resistant to linezolid and strains not susceptible to vancomycin or daptomycin (Table 4).[31,48–55]

In a Spanish study, it was observed that the minimum inhibitory concentration required to inhibit the growth of 50% of organisms (MIC_{50}) and minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC_{90}) of tedizolid, linezolid, daptomycin, and vancomycin against MRSA strains from blood cultures were 0.25 and 0.50 mcg/mL, 2 and 4 mcg/mL, 0.5 and 0.5 mcg/mL, and 1 and 2 mcg/mL, respectively.[49] In another study, the MIC of tedizolid ranged from 0.12 mcg/mL to 0.50 mcg/mL (MIC_{90} of 0.25 mcg/mL) against *S. aureus* strains from skin and soft tissue infections.[40] Similar results were reported in another study in *S. aureus* strains from skin and soft tissue infections, in which the MIC_{50}

Table 3 Proposed minimum inhibitory concentration (MIC) cut-off point and disc diffusions for tedizolid[48]

Microorganism	Cut-off points (S)	
	MIC (mcg/mL)	Disc diffusion using a disc of 20 or 10 mcg
Staphylococcus aureus	≤2	≥18
Coagulase-negative staphylococci	≤2	≥18
Enterococcus spp., *Streptococcus pneumoniae*, and *Streptococcus* spp. other than *S. pneumoniae*	≤2	≥15 mm
Corynebacterium jeikeium	≤2	No range recommended due to the reduced number of strains tested
Listeria monocytogenes	≤2	≥15 mm

Abbreviation: S, sensitive.

and MIC_{90} of tedizolid were 0.25 mg/L, regardless of whether the isolated strain showed resistance to methicillin.[55] These values were four- to eightfold lower than those observed with linezolid (MIC_{50} and MIC_{90} of 1 and 2 mg/L, respectively).

Similarly, tedizolid has shown excellent in vitro activity against 28 clinical strains of penicillin-resistant *Streptococcus pneumoniae* (MIC of penicillin G ≥ 2 mcg/mL), with MIC_{50} and MIC_{90} values of 0.25 mcg/mL.[56] These values were lower than those observed with linezolid (MIC_{50} and MIC_{90} of 0.5 mcg/mL and 1.0 mcg/mL, respectively). In another study, the MIC of tedizolid did not exceed the value of 0.25 and 0.12 mcg/mL against strains of *Streptococcus agalactiae* and *Streptococcus pyogenes,* respectively, from skin and soft tissue infections.[40]

Lastly, the MIC_{90} of tedizolid was between two and four times lower than that observed with linezolid against strains of enterococci (MIC_{90} of 1.0 mcg/mL and MIC_{90} of 0.5 mcg/mL against strains of enterococci sensitive and resistant to vancomycin, respectively).[50]

Strains resistant to linezolid (non-characterized resistance mechanisms)

Tedizolid has shown a high potency against strains of Gram-positive microorganisms resistant to linezolid (Table 4).[48,49,51–53] The MIC of tedizolid was ≤4 mcg/mL, ≤8 mcg/mL, and ≤16 mcg/mL in 88%, 96% and >99% of 120 strains not sensitive to linezolid (72 strains of *Enterococcus* spp. and *Streptococcus* spp., and 48 strains of *Staphylococcus* spp.), respectively.[53]

An MIC_{90} of 2 mcg/mL for tedizolid has been reported against strains of *S. aureus* resistant to linezolid.[51] In another study, the MIC of tedizolid was 0.5 mcg/mL against seven strains of MRSA (MIC against linezolid of 16 mcg/mL) and between 0.25 and 4.00 mcg/mL against five strains of coagulase-negative staphylococci from blood culture (MIC range of linezolid: 16–256 mcg/mL).[49] Similar results have been obtained in other studies.[51,52] In one of them, tedizolid showed an activity between eight and 16 times greater than linezolid against strains of *Staphylococcus* spp. resistant to linezolid, of which five strains of *S. aureus* also proved to be resistant to vancomycin and another five strains of the same species were not sensitive to daptomycin.[51] Similarly, tedizolid has shown an activity eight times greater than linezolid against strains of *Enterococcus* spp. resistant to linezolid.[51]

Despite the fact that tedizolid shows greater activity than vancomycin against strains of Gram-positive microorganisms resistant to linezolid,[53,54] the activity of glycopeptide has been shown to be greater in vitro against 40 strains of coagulase-negative staphylococci and one strain of *Streptococcus oralis* (MIC of vancomycin 1–2 mcg/mL vs MIC of tedizolid 1 to >32 mcg/mL, MIC of vancomycin 0.5 mcg/mL vs MIC of tedizolid 2 mcg/mL, respectively).[53]

Strains with characterized linezolid-resistance mechanisms

Tedizolid has maintained its activity against Gram-positive microorganisms with characterized resistance mechanisms against linezolid (Table 5).[51] Thus, tedizolid's potency has been observed to be between eight and 16 times greater than that of linezolid in strains of *S. aureus* that carry the G2576U[51] mutation (MIC of tedizolid 2–8 mcg/mL vs MIC of linezolid 16–64 mcg/mL), and approximately 16 times greater in strains of *S. aureus* which carry the *cfr* gene (MIC of tedizolid 0.5–1.0 mcg/mL vs MIC of linezolid 8–32 mcg/mL).

Another study reported MIC values for tedizolid of between 0.5 and 16.0 mcg/mL when it was tested against 39 strains of *Staphylococcus* spp. carrying the G2576U mutation (MIC of linezolid 8 to >32 mcg/mL) and between 0.5 and 8.0 mcg/mL when tested against four strains of *Staphylococcus* spp. carrying the *cfr* gene (MIC of linezolid 8 to >32 mcg/mL).[53] Similarly, the MIC of tedizolid was

Table 4 Activity of tedizolid (TR-700) and other antibiotics against Gram-positive microorganisms

Microorganism	Strains tested (n)	Antibiotic	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)	Range (mcg/mL)
Corynebacterium jeikeium	12[48]	Tedizolid	0.25	0.5	0.25–0.50
		Cefotaxime	32	32	8–32
		Levofloxacin	>16	>16	16 >16
		Linezolid	1	1	0.5–1.0
Enterococcus faecalis S to vancomycin	54[48] + 73[50] + 49[54]	TR-700[48,50,54]	0.25–0.50	0.5–1.0	0.12–1.0
		Linezolid[48,50,54]	2	2	0.5–4.0
		Vancomycin[50,54]	1–2	2	0.5–4.0
		Cefotaxime[48]	>64	>64	0.25 > 64.0
		Levofloxacin[48,54]	1–2	>16–64	0.5–64.0
		Ampicillin[54]	1	4	0.25–8.0
		Erythromycin[54]	4	>128	0.12 to >128.0
		Tetracycline[54]	64	64	0.5–128.0
		Teicoplanin[54]	0.25	0.5	≤0.12–0.50
E. faecalis R to vancomycin	45[48] + 49[50] + 12[54]	TR-700[48,50,54]	0.25–0.5	0.5	0.25–1.0
		Linezolid[48,50,54]	1–2	1–2	0.5–4.0
		Vancomycin[50,54]	>32 to >128	>32 to >128	4 to >128
		Cefotaxime[48]	>64	>64	0.25 to >64.0
		Levofloxacin[48,54]	>16–64	>16–64	0.5–128.0
		Ampicillin[54]	2	4	1–4
		Erythromycin[54]	>128	>128	>128
		Tetracycline[54]	32	64	0.5–64.0
		Teicoplanin[54]	64	64	32–128
E. faecalis R to linezolid	16[51] + 12[53]	TR-700[51,53]	2–4	4	0.5–8.0
		Linezolid[51]	32	32	8–32
		Vancomycin[51]	1	>16	1 to >16
Enterococcus faecium S to vancomycin	52[48] + 53[50] + 30[54]	TR-700[48,50,54]	0.25–0.5	0.25–1	0.06–2.00
		Linezolid[48,50,54]	2	2–4	0.5–4.0
		Vancomycin[50,54]	0.5–1.0	0.5–1.0	0.25–4.00
		Cefotaxime[48]	>64	>64	0.5 to >64
		Levofloxacin[48,54]	4–64	>16–64	0.5–128.0
		Ampicillin[54]	>128	>128	1 to >128
		Erythromycin[54]	>128	>128	0.25 to >128.00
		Tetracycline[54]	0.5	1	0.12–32.00
		Teicoplanin[54]	0.5	0.5	0.25–2.00
E. faecium R to vancomycin	52[48] + 51[50] + 29[54]	TR-700[48,50,54]	0.12–0.5	0.25–0.5	0.06–2.00
		Linezolid[48,50,54]	1–2	1–4	0.5 to >8.0
		Vancomycin[50,54]	>32–128	>32 to >128	8 to >128
		Cefotaxime[48]	>64	>64	>64
		Levofloxacin[48,54]	>16–64	>16–128	1–128
		Ampicillin[54]	>128	>128	64 to >128
		Erythromycin[54]	128	>128	64 to >128
		Tetracycline[54]	0.25	128	≤0.06–128.00
		Teicoplanin[54]	16	64	2–64
E. faecium R to linezolid	36[51] + 45[53]	TR-700[51,53]	2	2–4	0.5–8.0
		Linezolid[51]	32	64	4 to >128
		Vancomycin[53]	>16	>16	0.5 to >16
Listeria monocytogenes	33[48]	Tedizolid	0.25	0.25	0.25–0.50
		Cefotaxime	32	32	2–32
		Levofloxacin	1	1	1–2
		Linezolid	2	2	2–2
Staphylococcus aureus S to methicillin	105[48] + 95[50] + 30[54]	TR-700[48,50,54]	0.25–0.50	0.5	0.25–8.00
		Linezolid[48,50,54]	2–4	2–4	1 to >8
		Vancomycin[48,50,54]	0.5–1.0	1	0.25–2.00
		Oxacillin[48,50,54]	0.25–0.50	0.5	0.06–0.50

(*Continued*)

Table 4 (*Continued*)

Microorganism	Strains tested (n)	Antibiotic	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)	Range (mcg/mL)
		Cefotaxime[48]	2	2	0.03–4.00
		Levofloxacin[48,54]	0.25–0.50	1–4	0.12 to >16.00
		Erythromycin[48,54]	0.5	>128	0.5 to >128.0
		Clindamycin[48,54]	0.25	0.25	≤0.06–1.00
		Cotrimoxazole[48,54]	0.25	2	≤0.06–32.00
		Gentamycin[48,54]	0.5	128	0.06 to >128.00
		Tetracycline[48,54]	0.5	32	0.25–64.00
S. aureus S to methicillin**	39[55]	Tedizolid	0.25	0.25	0.12–0.50
		Linezolid	1	2	0.5–2.0
S. aureus R to methicillin	129[48] + 103[50] + 30[54]	TR-700[48,50,54]	0.5	0.5–1.0	0.12–16.0
		Linezolid[48,50,54]	2	4	1 to >8
		Vancomycin[50]	1	1	0.5–2.0
		Oxacillin[50,54]	32 to >128	32 to >128	4 to >128
		Cefotaxime[48]	16	>64	2 to >64
		Levofloxacin[48,54]	8–16	>16 to >128	0.12 to >128.00
		Erythromycin[48,54]	>128	>128	0.5 to >128.0
		Clindamycin[48,54]	>128	>128	0.25 to >128.00
		Cotrimoxazole[48,54]	0.5	>128	0.25 to >128.00
		Gentamycin[48,54]	64	>128	0.25 to >128.00
		Tetracycline[48,54]	64	64	0.5–128.0
S. aureus R to methicillin community-acquired	100[50]	TR-700	0.5	0.5	0.25–1.00
		Linezolid	2	4	1–4
		Vancomycin	4	4	1–4
		Oxacillin	32	32	4 to >32
S. aureus R to methicillin**	124[55]	Tedizolid	0.25	0.25	0.12–0.50
		Linezolid	1	2	0.5–2.0
S. aureus* S to linezolid	449[49]	TR-700	0.25	0.5	0.125–0.500
		Linezolid	2	2	≤0.25–4.00
		Daptomycin	0.25	0.5	≤0.125–1.000
		Vancomycin	1	1	≤0.5–4.0
		Teicoplanin	≤0.5	1	≤0.5–4.0
–*S. aureus* S to linezolid, S to oxacillin*	202[49]	TR-700	0.25	0.25	0.125–0.500
		Linezolid	1	2	≤0.25–4.00
		Daptomycin	0.25	0.5	≤0.125–1.000
		Vancomycin	1	1	≤0.5–2.0
		Teicoplanin	≤0.5	1	≤0.5–2.0
–*S. aureus* S to linezolid, R to oxacillin*	247[49]	TR-700	0.25	0.5	0.125–0.500
		Linezolid	2	4	≤0.25–4.00
		Daptomycin	0.5	0.5	≤0.125–1.000
		Vancomycin	1	2	≤0.5–4.0
		Teicoplanin	≤0.5	1	≤0.5–4.0
S. aureus R to linezolid*	7[49]	TR-700	0.5	NA	0.5
		Linezolid	16	NA	16
		Daptomycin	0.5	NA	0.5
		Vancomycin	2	NA	1–2
		Teicoplanin	1	NA	≤0.5–2.0
S. aureus R to linezolid	13[48] + 17[51] + 5[52]	Tedizolid[48,51,52]	0.25–4.00	0.2–8.0, NA[52]	0.12–16.00
		Cefotaxime[48]	>64	>64	2 to >64
		Levofloxacin[48]	>16	>16	0.25 to >16.00
		Linezolid[48,51,52]	2 to >8	>8–16, NA[52]	1–64
		Vancomycin[52]	1	NA	1
		Teicoplanin[52]	1	NA	≤0.5–2.0
		Daptomycin[52]	0.5	NA	0.5
		Tigecycline[52]	0.12	NA	0.12–0.25
		Quinupristin/ dalfopristin[52]	4	NA	1–4

(*Continued*)

Table 4 (*Continued*)

Microorganism	Strains tested (n)	Antibiotic	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)	Range (mcg/mL)
		Ciprofloxacin[52]	>4	NA	≤1 to >4
		Cotrimoxazole[52]	≤1	NA	≤1
		Tetracycline[52]	≤4	NA	≤4
		Erythromycin[52]	>4	NA	≤0.5 to >4.0
		Clindamycin[52]	>4	NA	>4
		Chloramphenicol[52]	>32	NA	16 to >32
		Gentamycin[52]	≤4	NA	≤4 to >16
		Tobramycin[52]	>16	NA	≤4 to >16
		Rifampicin[52]	≤1	NA	≤1 to >4
S. aureus not S to vancomycin	32[48]	Tedizolid	0.25	1	0.12–1.00
		Cefotaxime	>64	>64	2 to >64
		Levofloxacin	16	>16	4 to >16
		Linezolid	2	4	1–4
Coagulase-negative staphylococci**	7[55]	Tedizolid	NA	NA	0.12–0.25
		Linezolid	NA	NA	0.5–1.0
Coagulase-negative staphylococci S to linezolid*	199[a,49]	TR-700	0.25	0.25	≤0.03–0.50
		Linezolid	1	2	≤0.25–4.00
		Daptomycin	0.25	0.5	≤0.125–1.000
		Vancomycin	2	2	≤0.5–4.0
		Teicoplanin	2	8	≤0.5–32.0
–Coagulase-negative staphylococci S to linezolid, S to oxacillin*	41[49]	TR-700	0.25	0.25	0.06–0.25
		Linezolid	1	2	≤0.25–2.00
		Daptomycin	0.25	0.5	≤0.125–0.500
		Vancomycin	2	2	≤0.5–2.0
		Teicoplanin	2	4	≤0.5–8.0
–Coagulase-negative staphylococci S to linezolid, R to oxacillin*	158[49]	TR-700	0.125	0.25	≤0.03–0.50
		Linezolid	1	2	≤0.25–4.00
		Daptomycin	0.25	0.5	≤0.125–1.000
		Vancomycin	2	2	≤0.5–4.0
		Teicoplanin	2	8	≤0.5–32.0
Coagulase-negative staphylococci R to linezolid	5[b,49]	TR-700	2	NA	0.25–4.00
		Linezolid	16	NA	16–256
		Daptomycin	0.5	NA	0.25–0.50
		Vancomycin	2	NA	1–2
		Teicoplanin	4	NA	1–16
Coagulase-negative staphylococci S to methicillin	46[48] + 29[54]	Tedizolid[48,54]	0.25–0.50	0.5	0.12–1.0
		Cefotaxime[48]	0.5	2	0.03–4.00
		Levofloxacin[48,54]	0.25–0.50	0.5	0.06–32.00
		Linezolid[48,54]	1–2	2–4	0.5–4.0
		Erythromycin[54]	0.5	128	0.25 to >128.00
		Clindamycin[54]	0.25	1	0.12 to >128.00
		Cotrimoxazole[54]	0.25	16	≤0.06–32.00
		Gentamycin[54]	0.12	64	0.06–128.00
		Tetracycline[54]	0.5	32	0.5–128.0
		Oxacillin[54]	0.12	0.25	0.06–0.25
		Vancomycin[54]	1	1	0.5–2.0
Coagulase-negative staphylococci R to methicillin	58[48] + 26[54]	Tedizolid[48,54]	0.25–0.50	0.5	0.12–1.00
		Cefotaxime[48]	8	>64	0.5 to >64.0
		Levofloxacin[48,54]	0.5–8.0	≥16	0.12 to >16.00
		Linezolid[48,54]	1–2	2–4	0.5–8.0
		Erythromycin[54]	64	128	≤0.06 to >128.00
		Clindamycin[54]	0.25	>128	0.12 to >128.00
		Cotrimoxazole[54]	2	32	≤0.06–32.00
		Gentamycin[54]	16	64	0.06–128.00

(*Continued*)

Table 4 (*Continued*)

Microorganism	Strains tested (n)	Antibiotic	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)	Range (mcg/mL)
		Tetracycline[54]	4	128	0.5 to >128.0
		Oxacillin[54]	4	64	0.5 to >128.0
		Vancomycin[54]	1	2	0.25–2.00
Coagulase-negative staphylococci not S to linezolid	40[c,53]	TR-700	4	16	1 to >32
		Vancomycin	2	2	1–2
Coagulase-negative staphylococci R to linezolid	6[d,51] + 164[e,52]	TR-700[51,52]	NA,[51] 4[52]	NA,[51] 8[52]	0.06–16.00
		Linezolid[51,52]	NA,[51] 128[52]	NA,[51] >128[52]	8 to >128
		Vancomycin[52]	2	4	1–4
		Teicoplanin[52]	4	16	≤0.5–64
		Daptomycin[52]	0.5	1	0.25–2.00
		Tigecycline[52]	0.25	0.5	≤0.06–0.50
		Quinupristin/ dalfopristin[52]	1	2	≤0.25–16.00
		Ciprofloxacin[52]	>4	>4	≤1 to >4
		Cotrimoxazole[52]	>4	>4	≤1 to >4
		Tetracycline[52]	≤4	≤4	≤4 to >16
		Erythromycin[52]	>4	>4	≤0.5 to >4.0
		Clindamycin[52]	>4	>4	≤0.5 to >4.0
		Chloramphenicol[52]	>32	>32	≤8 to >32
		Gentamycin[52]	>16	>16	≤4 to >16
		Tobramycin[52]	>16	>16	≤4 to >16
		Rifampicin[52]	>4	>4	≤1 to >4
Staphylococcus epidermidis S to methicillin	48[50]	TR-700	0.25	0.5	0.12–1.00
		Linezolid	1	2	0.5–4.0
		Vancomycin	2	2	1–4
		Oxacillin	0.12	0.25	0.06–0.25
S. epidermidis R to methicillin	72[50]	TR-700	0.25	0.5	0.12–1.00
		Linezolid	1	2	0.5–4.0
		Vancomycin	2	2	0.25–4
		Oxacillin	16	>32	0.5 ≥ 32
S. epidermidis R to linezolid	19[51]	TR-700	4	8	2 to >64
		Linezolid	32	>128	16 to >128
Beta-hemolytic streptococci	202[f,48]	Tedizolid	0.25	0.25	0.12–0.5
		Cefotaxime	0.03	0.06	0.015–0.06
		Levofloxacin	0.5	1	0.25–2.00
		Linezolid	1	2	1–4
Streptococcus agalactiae	52[50] + 15[54]	TR-700[50,54]	0.25	0.5	0.06–1.00
		Linezolid[50,54]	2	2	1–2
		Vancomycin[50]	0.5	0.5	0.25–1.00
		Penicillin G[54]	0.06	0.06	0.03–0.06
		Cefotaxime[54]	0.06	0.06	0.03–0.06
		Clindamycin[54]	0.25	>128	0.25 to >128.00
		Erythromycin[54]	0.5	>128	0.25 to >128.00
		Levofloxacin[54]	1	2	1–2
Streptococcus pneumoniae S to penicillin	53[48] + 38[50]	TR-700[48,50]	0.25	0.25	0.03–0.50
		Linezolid[48,50]	1	1–2	0.12–2.00
		Vancomycin[50]	0.25	0.5	0.12–1.00
		Cefotaxime[48]	0.015	0.03	0.015–0.250
		Levofloxacin[48]	1	1	0.25–4.00
S. pneumoniae I to penicillin	26[48] + 37[50]	TR-700[48,50]	0.25	0.25–0.50	0.06–0.50
		Linezolid[48,50]	1	1–2	0.5–4.0
		Vancomycin[50]	0.25	0.5	0.25–0.50
		Cefotaxime[48]	0.12	0.5	0.03–1.00
		Levofloxacin[48]	1	1	0.5–1.0

(*Continued*)

Table 4 (*Continued*)

Microorganism	Strains tested (n)	Antibiotic	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)	Range (mcg/mL)
S. pneumoniae R to penicillin	54[48] + 35[50]	TR-700[48,50]	0.25	0.25	0.06–0.50
		Linezolid[48,50]	1	1–2	0.25–2.00
		Vancomycin[50]	0.25	0.5	0.12–1.00
		Cefotaxime[48]	1	8	0.5–8.0
		Levofloxacin[48]	1	1	0.5–2.0
Streptococcus pyogenes	102[50] + 15[54]	TR-700[50,54]	0.12–0.25	0.25–0.50	0.06–0.50
		Linezolid[50,54]	1	2	0.06–2.00
		Vancomycin[50]	0.5	0.5	0.25–1.00
		Penicillin G[54]	0.015	0.015	≤0.008–0.015
		Cefotaxime[54]	0.015	0.03	≤0.008–0.030
		Clindamycin[54]	0.12	0.25	0.12–0.25
		Erythromycin[54]	0.12	0.25	0.12–0.25
		Levofloxacin[54]	1	4	0.5–4
Streptococcus viridans	30[48]	Tedizolid	0.25	0.25	0.06–0.50
		Cefotaxime	0.12	0.5	0.015–2.000
		Levofloxacin	1	2	0.25–2.00
		Linezolid	2	2	0.5–2.0

Notes: *Blood culture strains; **skin and skin-structure infection strains; [a]*Staphylococcus epidermidis*: 135, *Staphylococcus hominis*: 40, *Staphylococcus haemolyticus*: 19, *Staphylococcus lugdunensis*: 3, *Staphylococcus intermedius*: 1, *Staphylococcus warneri*: 1; [b]*S. epidermidis*: 2, *S. hominis*: 2, *S. haemolyticus*: 1; [c]*Staphylococcus capitis*: 2, *S. epidermidis*: 29, *S. haemolyticus*: 5, *Staphylococcus simulans*: 2, *Staphylococcus xylosus*: 2; [d]*S. hominis*: 1, *Staphylococcus sciuri*: 5; [e]*S. epidermidis*: 142, *S. hominis*: 15, *S. warneri*: 7; [f]*Streptococcus agalactiae*: 101, *Streptococcus pyogenes*: 101. **In bold:** *Staphylococcus aureus* S to linezolid* group includes 202 strains of *S. aureus* S to linezolid, S to oxacillin* and 247 strains of *S. aureus* S to linezolid, R to oxacillin*. Coagulase-negative staphylococci S to linezolid* group includes 41 strains of coagulase-negative staphylococci S to linezolid, S to oxacillin* and 158 strains of coagulase-negative staphylococci S to linezolid, R to oxacillin*. Data from Brown and Traczewski,[48] Betriu et al,[49] Schaadt et al,[50] Shaw et al,[51] Rodríguez-Avial et al,[52] Jones et al,[53] Yum et al,[54] Prokocimer et al.[55]

Abbreviations: S, sensitive; I, intermediate sensitivity; R, resistant; NA, not applicable; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of organisms; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of organisms.

between 2 and 4 mcg/mL against seven strains of *Enterococcus faecium* and one strain of *Enterococcus faecalis* carrying the G2576U mutation, compared with an MIC for linezolid of between 16 and 32 mcg/mL.[51] Another study reported MIC values for tedizolid between 0.5 and 8.0 mcg/mL when tested against 69 strains of *Enterococcus* spp. carrying the G2576T mutation (MIC of linezolid 4 to >32 mcg/mL).[53]

In another study, resistance to tedizolid was observed in only three of the 36 strains of *Enterococcus* spp. resistant to linezolid analyzed.[57] Two of them were strains of *E. faecium* homozygous for the G2576T mutation (MIC against tedizolid of 8 mcg/mL), while no resistance mechanism could be established in the third strain of this same species (MIC against tedizolid of 16 mcg/mL).

Aerobic Gram-negative microorganisms

Tedizolid shows a limited activity against strains of *Haemophilus influenzae* and *Moraxella catarrhalis* (MIC_{90} of 16 and 4 mcg/mL, respectively) (Table 6).[50] Both tedizolid and linezolid have shown a lower activity than that of cefotaxime and levofloxacin against strains of these microorganisms.[48] However, the MIC_{90} of tedizolid was two times lower than that observed for linezolid (MIC_{90} for linezolid of 32 and 8 mcg/mL, respectively).[50]

Anaerobic microorganisms

The activity of tedizolid against anaerobic microorganisms has been reported to be greater than or equal to that observed with linezolid (Table 7).[50]

Acid-fast bacilli

Tedizolid has shown excellent activity against 95 strains of *Mycobacterium tuberculosis*, nine of which showed resistance to isoniazid or rifampicin and 25 to both tuberculostatics.[58] The MIC_{50} was 0.25 mcg/mL and the MIC_{90} was 0.50 mcg/mL for all the strains. Additionally, the MIC_{50} and MIC_{90} values of tedizolid phosphate were 0.5 mcg/mL against ten strains of sensitive *M. tuberculosis* and ten strains of *M. tuberculosis* resistant to tuberculostatics.

Resistance mechanisms

Several oxazolidinone resistance mechanisms have been described, including mutations in domain V of 23S rRNA[59,60] and horizontal transmission of the *cfr* gene.[17,18] However, a number of ribosomal proteins of the 50S subunit have regions that interact with the oxazolidinone-binding site in the peptidyl transferase center, most notably L3 and L4. Mutations in the genes that encode these proteins may have an impact on the sensitivity presented by different microorganisms to this family

Table 5 Activity of tedizolid (TR-700) and other antibiotics against Gram-positive microorganisms with characterized linezolid-resistance mechanisms

Microorganism	Strains tested (n)	Antibiotic	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)	Range (mcg/mL)
G2576T					
Enterococcus spp.	69[a,53]	TR-700	2	2	0.5–8
		Linezolid	8	16	4–32
		Ciprofloxacin	>4	>4	1 to >4
		Daptomycin	1	2	0.12–4.00
		Erythromycin	>2	>2	≤0.25 to >2.0
		Quinupristin/dalfopristin	1	>2	≤0.25 to >2.0
		Teicoplanin	>16	>16	≤0.12 to >16.00
		Tetracycline	≤2	>8	≤2 to >8
		Vancomycin	>16	>16	0.5 to >16.0
Staphylococcus spp.	39[b,53]	TR-700	4	8	0.5–16.0
		Linezolid	16	>32	8 ≥ 32
		Ciprofloxacin	>4	>4	0.25 to >4.00
		Clindamycin	1	>2	≤0.25 to >2.00
		Daptomycin	0.25	0.5	0.25–1.00
		Erythromycin	>2	>2	≤0.25 to >2.00
		Gentamicin	>8	>8	≤2 to >8
		Oxacillin	>2	>2	≤0.25 to >2.00
		Quinupristin/dalfopristin	0.5	1	≤0.25–2.00
		Teicoplanin	4	8	0.5–16.0
		Tetracycline	≤2	>8	≤2 to >8
		Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 to >2.0
		Vancomycin	2	2	0.5–2.0
***cfr* gene**					
Staphylococcus spp.	4[c,53]	TR-700	1	–	0.5–8.0
		Linezolid	32	–	8 to >32
		Ciprofloxacin	>4	–	>4
		Clindamycin	>4	–	>4
		Daptomycin	≤0.25	–	≤0.25
		Erythromycin	≤0.25	–	≤0.25 to >2.00
		Gentamicin	>8	–	≤2 to >8
		Oxacillin	>2	–	>2
		Quinupristin/dalfopristin	>2	–	1 to >2
		Teicoplanin	≤2	–	≤2
		Tetracycline	≤2	–	≤2 to >8
		Trimethoprim/sulfamethoxazole	>2	–	≤0.5 to >2.0
		Vancomycin	1	–	1–2

Notes: [a]*Enterococcus faecalis*: 15, *Enterococcus faecium*: 54; [b]*Staphylococcus aureus*: 6, *Staphylococcus epidermidis*: 22, *Staphylococcus capitis*: 2, *Staphylococcus haemolyticus*: 5, *Staphylococcus simulans*: 2, *Staphylococcus xylosus*: 2; [c]*S. aureus*: 2, *S. epidermidis*: 2.
Data from Jones et al.[53]
Abbreviations: MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of organisms; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of organisms.

of antibiotics. L3 mutations were first associated with reduced susceptibility to oxazolidinones in a study that sequenced the *rplC* gene, encoding L3, in eleven clinical isolates resistant to linezolid.[61] The sequence analysis identified two L3 mutations, ΔSer145 in *S. aureus* strain NRS127 and Ala157Arg in *Staphylococcus epidermidis* strain 1653059, both adjacent to the oxazolidinone-binding site in the peptidyl transferase center. Tedizolid maintained an eight- to 16-fold potency advantage over linezolid against strains NRS127 (MIC 1 vs 8 mcg/mL) and 1653059 (MIC 16 vs 256 mcg/mL). Another study of MRSA clinical isolates resistant to linezolid and carrying the *cfr* gene identified mutations in L3, including ΔSer145/His146Tyr and ΔMet169-Gly174.[62] The MICs of tedizolid were between 1 and 2 mcg/mL, while those of linezolid were between 32 and 64 mcg/mL, respectively.

A study analyzed the structure–activity relationship of different oxazolidinones against strains of *S. aureus* resistant to linezolid due to ribosomal mutations (23S rRNA, L3, L4) or due to methylation of 23S rRNA via horizontal transfer of the *cfr* gene.[63] According to the MIC values observed in this

Table 6 Activity of tedizolid and other antibiotics against Gram-negative microorganisms

Microorganism	Strains tested (n)	Antibiotic	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)	Range (mcg/mL)
All Haemophilus influenzae	99[48] + 25[54]	Tedizolid[48,54]	2–8	4–16	2–32
		Cefotaxime[48,54]	0.015–0.030	0.5	≤0.008–2.000
		Levofloxacin[48,54]	0.12	0.12	0.12
		Linezolid[48,54]	≥8	>8–16	4–16
		Ampicillin[54]	>128	>128	0.5 to >128.0
		Ampicillin/sulbactam[54]	4	8	0.5–8.0
		Cefaclor[54]	4	>128	2 to >128
		Cefuroxime[54]	1	>128	0.25 to >128.0
		Azithromycin[54]	4	4	2–4
		Cotrimoxazol[54]	4	32	≤0.06–32.00
		Tetraciclina[54]	0.5	8	0.25–32.00
Beta-lactamase-negative *H. influenzae*	32[48]	Tedizolid	8	16	4–32
		Cefotaxime	0.008	0.015	0.008–0.030
		Levofloxacin	0.12	0.12	0.12
		Linezolid	>8	>8	4 to >8
Beta-lactamase-positive *H. influenzae*	42[48]	Tedizolid	8	32	4–32
		Cefotaxime	0.015	0.015	0.008–0.030
		Levofloxacin	0.12	0.12	0.12
		Linezolid	>8	>8	8 to >8
Beta-lactamase-negative *H. influenzae*, not sensitive to ampicillin	25[48]	Tedizolid	8	16	2–16
		Cefotaxime	0.5	0.5	0.03–2.00
		Levofloxacin	0.12	0.12	0.12
		Linezolid	>8	>8	>8 to >8
Moraxella catarrhalis	50[48] + 27[54]	Tedizolid[48,54]	1–4	1–4	0.5–4
		Cefotaxime[48]	0.250	1	0.03–2
		Levofloxacin[48,54]	0.06	0.06	0.03–0.06
		Linezolid[48,54]	4–8	4–8	2–16
		Penicillin G[54]	16	32	0.03–32
		Cefaclor[54]	2	8	0.25–32
		Clindamycin[54]	2	4	1–4
		Erythromycin[54]	0.25	0.5	0.12–0.5
		Tetracycline[54]	0.5	0.5	0.25–16

Data from Brown and Traczewski[48] and Yum et al.[54]

Abbreviations: MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of organisms; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of organisms.

study, the C and D rings play a fundamental role in the activity of the antimicrobial, both in strains with ribosomal mutations and in strains that carry the *cfr* gene. As has been suggested previously, the C and D rings of the tedizolid molecule may act as additional hydrogen bond donors to the sugar backbone of residues A2451 and U2584 of rRNA.[51] Furthermore, the presence of both 1,2,3-triazole and hydroxymethyl substituents on C-5 of ring A maintained the potency of the antibiotic against strains carrying the *cfr* gene, while the presence of acetamide substituents was associated with a fourfold increase in the MIC value of the antimicrobial.[63]

The structure of linezolid does not contain the D ring and has an acetamide substituent on C-5 of ring A, unlike tedizolid, whose structure contains a D ring and a hydroxymethyl substituent on C-5 of ring A. These structural features explain why tedizolid maintains activity against strains with high MICs of linezolid, especially those strains that carry the *cfr* gene. In the same study, the *S. aureus* MIC values of tedizolid were 0.5 to 1.0 mcg/mL against strains carrying ribosomal mutations (vs 2 to 32 mcg/mL for linezolid) and 0.5 mcg/mL against all *cfr*-positive strains tested (vs 2 to 16 mcg/mL for linezolid).[63]

The potential for *S. aureus* to develop resistance to tedizolid was investigated in a study using representative MSSA and MRSA strains through determination of spontaneous mutation frequencies and by serial passage on antibiotic gradient plates containing tedizolid or linezolid.[64] The median spontaneous mutation frequency that resulted in a reduction in sensitivity to tedizolid was 1.1×10^{-10} for the MSSA strain and 1.9×10^{-10} for the MRSA strain. These values were approximately 16-fold lower than those obtained for linezolid (2.0×10^{-9} for MSSA and 3.0×10^{-9} for MRSA). The spontaneous mutant strains selected with tedizolid possessed the T2500A 23S rRNA mutation or Gly155Arg, Gly155Arg/Met169 Leu, or ΔPhe127-His146 mutations in

Table 7 Activity of tedizolid and other antibiotics against anaerobic microorganisms

Microorganism	Strains tested (n)	Antibiotic	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)	Range (mcg/mL)
Bacteroides fragilis	10[50] + 30[54]	TR-700[50,54]	2–4	2–4	1–4
		Linezolid[50,54]	4	4	2–4
		Metronidazole[50,54]	0.12–4.00	1–4	0.12 to >32.00
		Imipenem[50,54]	0.12–0.25	0.5–1.0	≤0.06–4.00
		Ampicillin[54]	32	>128	16 to >128
		Ampicillin/sulbactam[54]	2	16	1–32
		Piperacillin[54]	32	256	4 to >256
		Piperacillin/tazobactam[54]	0.25	1	0.12–8.00
		Cefoxitin[54]	8	32	4–64
		Cefotetan[54]	8	32	4–128
		Clindamycin[54]	128	>128	≤0.06 to >128.00
Bacteroides vulgatus	10[50]	TR-700	2	4	1–8
		Linezolid	2	4	2–4
		Metronidazole	0.25	0.25	0.12–0.50
		Imipenem	0.25	0.5	0.25–0.50
Bacteroides thetaiotaomicron	10[50] + 15[54]	TR-700[50,54]	2	2	1–2
		Linezolid[50,54]	4	4–8	4–8
		Metronidazole[50,54]	1–4	1–4	0.5 to >32
		Imipenem[50,54]	0.25–0.50	1–2	0.12–4
		Ampicillin[54]	32	>128	16 to >128
		Ampicillin/sulbactam[54]	1	32	1–32
		Piperacillin[54]	32	>256	16 to >256
		Piperacillin/tazobactam[54]	4	8	2–16
		Cefoxitin[54]	16	32	16–32
		Cefotetan[54]	128	>128	32 to >128
		Clindamycin[54]	8	>128	2 to >128
Bacteroides ovatus	10[50]	TR-700	2	8	0.06–8.00
		Linezolid	8	8	0.5–8.0
		Metronidazole	1	1	0.5 to >32.0
		Imipenem	0.25	0.5	0.06–0.50
Clostridium perfringens	10[50] + 15[54]	TR-700[50,54]	0.25–0.50	0.25–2.0	0.12–2.00
		Linezolid[50,54]	2	2–4	1–2
		Metronidazole[50,54]	1–4	4 to >32	1 to >32
		Imipenem[50,54]	≤0.06–0.12	≤0.06–0.50	≤0.06–1.00
		Ampicillin[54]	≤0.06	0.12	≤0.06–0.50
		Ampicillin/sulbactam[54]	≤0.06	0.25	≤0.06–0.50
		Piperacillin[54]	≤0.06	0.25	≤0.06–1.00
		Piperacillin/tazobactam[54]	≤0.06	≤0.06	≤0.06
		Cefoxitin[54]	0.5	1	0.25–1.00
		Cefotetan[54]	≤0.06	0.12	≤0.06–0.50
		Clindamycin[54]	1	2	≤0.06–2.00
		Vancomycin[54]	0.5	0.5	0.5–2.0
Peptostreptococcus spp.	59[a,54]	Tedizolid	0.06	0.25	0.03–0.25
		Linezolid	0.5	1	0.25–2.00
		Ampicillin	0.12	1	≤0.06–16.00
		Ampicillin/sulbactam	0.12	1	≤0.06–8.00
		Piperacillin	≤0.06	8	≤0.06–16.00
		Piperacillin/tazobactam	≤0.06	8	≤0.06–16.00
		Cefoxitin	0.25	4	≤0.06–16.00
		Cefotetan	0.5	16	≤0.06–128.00
		Imipenem	≤0.06	0.12	≤0.06–1.00
		Clindamycin	0.5	64	≤0.06 to >128.00
		Metronidazole	1	2	≤0.06–4.00
		Vancomycin	0.25	0.5	≤0.12–1.00
Peptostreptococcus anaerobius	10[50]	TR-700	0.25	0.5	0.12–0.50
		Linezolid	1	2	0.5–8

(*Continued*)

Table 7 (*Continued*)

Microorganism	Strains tested (n)	Antibiotic	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)	Range (mcg/mL)
		Metronidazole	0.5	1	≤0.06–1.00
		Imipenem	0.06	1	≤0.03–1.00
Peptostreptococcus micros	10[50]	TR-700	0.25	0.5	0.12–1.00
		Linezolid	1	2	0.5–2.0
		Metronidazole	≤0.06	>32	≤0.06 to >32.00
		Imipenem	≤0.03	≤0.03	≤0.03 to ≤0.06
Porphyromonas asaccharolytica	10[50]	TR-700	0.25	0.5	0.25–0.50
		Linezolid	1	2	0.5–2
		Metronidazole	1	1	0.5–2
		Imipenem	<0.03	0.06	≤0.03 to ≤0.06
Prevotella spp.	20[50]	TR-700	1	4	≤0.06–16.00
		Linezolid	2	4	0.25–16.00
		Metronidazole	0.5	>32	≤0.06 to >32.00
		Imipenem	≤0.06	1	≤0.03–16.00

Notes: [a]*Finegoldia magna*: 19, *Peptoniphilus asaccharolyticus*: 15, *Peptostreptococcus anaerobius*: 12, *Peptostreptococcus micros*: 7, *Anaerococcus prevotii*: 6. Data from Schaadt et al[50] and Yum et al.[54]

Abbreviations: MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of organisms; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of organisms.

L3. Linezolid-selected spontaneous mutants possessed the T2500A or G2447T 23S rRNA mutations or the Gly155Arg or Gly155Arg/Met169 Leu L3 mutations.

Following 30 serial passages on antibiotic gradient plates, the MIC of tedizolid against the MSSA strain remained at 0.5 mcg/mL whereas the MIC of linezolid increased from 2 to 128 mcg/mL. Reduced sensitivity to linezolid was observed after five serial passages in a medium with linezolid, associated with the Gly155Arg mutation in L3. Subsequent passages in this medium resulted in mutant strains of MSSA that had the 23S rRNA G2447T mutation alone or the G2447T mutation coupled with the Gly152Asp mutation in L3. After serial passage of the MRSA strain, tedizolid MIC values increased eightfold (from 0.25 to 2.00 mcg/mL) while the MIC of linezolid increased 32-fold (from 1 to 32 mcg/mL). The reduction in sensitivity of the MRSA strain to linezolid was associated initially with the Lys68Gln mutation in L4 and later by the G2576T mutation in 23S rRNA, while resistance to tedizolid was associated with a T25761C/G2576T double mutation in 23S rRNA.[64]

A second resistance-selection study passaged eight linezolid-susceptible strains through a medium containing tedizolid. A twofold increase in the MIC of tedizolid after 14 days was found in three of the strains: MSSA, VanA-phenotype *E. faecalis*, and *S. pyogenes* carrying the *erm(A)* gene. All tedizolid MIC values were less than or equal to 0.5 mcg/mL at the end of the experiment and all returned to baseline following passage in nonselective media.[53]

According to the results of the studies described to date, tedizolid has a more favorable resistance profile than linezolid.[53,64]

Animal studies

Studies in murine models have evaluated antibacterial activity, pharmacokinetics, and pharmacodynamic correlates of efficacy to determine exposure–response relationships for tedizolid. A dose-range study of tedizolid phosphate in a neutropenic mouse-thigh model of MSSA and MRSA infections with linezolid as a comparator, determined that AUC_{free}/MIC is the main determinant of efficacy.[34] For MSSA strains, the administration of a mean dose of tedizolid phosphate/tedizolid of 37.7 mg/kg/day resulted in stasis and a mean dose of 66.9 mg/kg/day resulted in the reduction of 1 log colony-forming unit (CFU)/g at 24 hours. Similarly, the administration of a mean dose of tedizolid phosphate/tedizolid of 35.3, 46.6, and 71.1 mg/kg/day resulted in stasis, reduction of 1 log CFU/g, and reduction of 2 log CFU/g at 48 hours, respectively. Additionally, for MRSA strains, the administration of a mean dose of tedizolid phosphate of 36.2 mg/kg/day resulted in stasis and a mean dose of 58.0 mg/kg/day resulted in the reduction of 1 log CFU/g at 24 hours. Similarly, the administration of a mean dose of tedizolid phosphate of 39.8, 52.4, and 105.0 mg/kg/day resulted in stasis, reduction of 1 log CFU/g and reduction of 2 log CFU/g at 48 hours, respectively. There were no differences in the doses of tedizolid phosphate needed to reach these values for strains of MSSA and MRSA. When compared with linezolid, the administration of doses up to 150 mg/kg/day resulted in bacterial densities in the

mouse thigh of approximately 1 log CFU/g higher than the stasis values.

An in vitro study showed that tedizolid accumulated inside the macrophages and reached a ratio of approximately 10 between the intracellular and extracellular concentration.[65] The value of this ratio was 1–2 for linezolid. Based on this finding, the objective of another study was to evaluate the effect of granulocytes in the activity of tedizolid in a murine model infected with strain 33591 of MRSA compared with the same neutropenic infection model.[66] It used doses of tedizolid phosphate equivalent to those humans would be given, ranging from 200 to 3200 mg daily. The animals were evaluated at 24, 48, and 72 hours after starting treatment. In the animals with a normal immune system, bacteriostasis was obtained at an equivalent dose in humans of slightly above 100 mg daily after 24 hours and less than 100 mg per day at 48-hour and 72-hour endpoints. The dose equivalent to 1200 mg given daily in humans obtained the maximum response after 24 hours and the dose equivalent to 800 mg given daily in humans obtained the maximum response after 48 hours. Lastly, the dose equivalent to 200 mg administered daily in humans produced a near-maximal effect after 72 hours, with no significant differences observed compared with the dose of 3200 mg daily. In contrast, in the neutropenic animals, bacteriostasis was achieved using a dose equivalent to slightly under 2300 mg given daily in humans after 24 hours and a dose slightly under 2000 mg daily after 72 hours. The dose equivalent to 3200 mg administered in humans was associated with maximum response.

Furthermore, a reduction in the colony counts of *S. aureus* strains was observed in immunocompetent mice after the administration of a dose equivalent to 200 mg of tedizolid phosphate given in humans, whereas an increase of 1 log CFU/g was observed in the granulocytopenic animals. This difference revealed that the antibiotic effect was mediated by the granulocytes.[66]

In another study, the effective dose for 50% of people (ED50) value of IV tedizolid phosphate was 2.8 mg/kg in a murine model with systemic MRSA infection and 3.3 mg/kg when this infection was caused by MSSA, while the ED50 of oral tedizolid phosphate was 3.7 mg/kg in the murine model with systemic MRSA infection and 5 mg/kg when this infection was caused by MSSA.[31] These values were lower than those observed with linezolid. However, no differences were observed between the efficacy of tedizolid and linezolid in a murine model infected with five strains of *S. aureus,* four of which showed resistance to methicillin.[67] Thus, exposure to tedizolid reduced the number of CFUs to 1.04–1.80 log10 at 24 hours, 2.13–2.68 log10 at 48 hours, and 2.68–3.72 log10 at 72 hours, while exposure to linezolid reduced the number of CFUs to 1.36–2.02 log10 at 24 hours, 2.19–3.11 log10 at 48 hours, and 2.64–3.76 log10 at 72 hours. Statistically significant differences were observed in the number of CFUs for some *S. aureus* strains at 24, 48, or 72 hours, although they were not consistent throughout the study period.

Tedizolid has shown in vitro activity against strains of *Nocardia brasiliensis,* with MIC_{50} and MIC_{90} values of 1 mg/L,[58] and both tedizolid and tedizolid phosphate have shown a high capacity for inhibiting intracellular growth of *N. brasiliensis* in vitro.[68] Therefore, the objective of one study was to evaluate the activity of two different doses of tedizolid phosphate (5 or 25 mg/kg), in monotherapy or combined with trimethoprim/sulfamethoxazole, in a murine model of actinomycosis due to *N. brasiliensis*.[69] Linezolid was used as a comparator treatment and saline solution as a control. At the end of treatment, statistically significant differences were observed in the degree of infection between all groups that received the different antibiotic treatments and the control group ($P = 0.004$). However, a greater response was observed in the groups that received tedizolid phosphate at a dose of 25 mg/kg, both in monotherapy and in combination with trimethoprim/sulfamethoxazole, than in the groups that received the other treatments.

Another study evaluated the activity of tedizolid phosphate at doses of 5, 12.5, and 25 mg/kg in a murine model of actinomycosis due to *N. brasiliensis*.[70] Saline solution was used as a control. The animals received the treatment 1 week after infection for a period of 3 weeks. Subsequently, the treatment was suspended for 1 week and started again for another 3 weeks. At the end of treatment, statistically significant differences were observed in the degree of infection between the control group and the groups that received the three doses of tedizolid phosphate ($P < 0.001$).

One study assessed survival at 7 days in a murine model with systemic infection with penicillin-resistant *S. pneumoniae* after administration of tedizolid phosphate orally or intravenously at different doses.[56] Four strains of penicillin-resistant *S. pneumoniae* were used (DR9, DR10, DR11, and DR14) and linezolid was used as a comparator treatment. The ED50 of tedizolid phosphate administered orally ranged from 5.7 mg/kg/day for the mice infected with DR9 to 11.53 mg/kg/day for those infected with DR14. This latter value was equivalent to that observed with linezolid, while the values compared with the rest of the strains were lower. Similarly, the ED50 of tedizolid phosphate administered intravenously ranged from 4.89 mg/kg/day in mice infected

with DR9 to 10.19 mg/kg/day for those infected with DR11. These values were lower than those observed with linezolid against the four strains of penicillin-resistant *S. pneumoniae*.

Clinical efficacy

To date, there have been a limited number of studies in humans evaluating the efficacy of tedizolid phosphate or tedizolid in skin and soft tissue infections, and some of these are still underway. The objective of one Phase II randomized double-blind clinical trial was to evaluate the efficacy of tedizolid phosphate administered at doses of 200, 300, or 400 mg once daily for 5–7 days in patients with complicated skin and soft tissue infections.[40] These included abscesses (with at least 2 cm of surrounding induration or requiring incision and drainage), surgical or posttraumatic wounds, and deep extensive cellulitis. A total of 192 patients were randomized between September 2008 and January 2009, of whom 188 received at least one dose of tedizolid phosphate and these 188 patients presented with a diagnosis of complicated skin and soft tissue infection (modified intent-to-treat and clinical modified intent-to-treat, respectively). Of the 188, 164 were included in the clinically evaluable population, 154 in the microbiological modified intent-to-treat population, and 133 in the microbiologically evaluable population. *S. aureus* strains were isolated in 139 (90.3%) of the 154 patients in whom a baseline Gram-positive microorganism was isolated, of which 80.6% were MRSA. The clinical cure rate in clinically evaluable patients was 98.2% for the group that received 200 mg of tedizolid phosphate and 94.4% for the group that received 300 or 400 mg of the antibiotic; no differences were observed in terms of the type and size of the lesion or the severity of the infection. Likewise, the clinical cure rate in microbiologically evaluable patients in whom *S. aureus* strains (n = 119) had been isolated was 96.6%, reaching a value of 96.8% when the isolated strains were MRSA. Clinical failure was observed in seven patients (3.7%).

In addition, the overall microbiological eradication rate was 97.7% in the microbiologically evaluable patients (n = 133), with no differences observed in terms of dose. This rate ranged from 92.6% to 100% when MRSA strains were isolated and from 88.9% to 100% when MSSA strains were isolated. Emerging pathogenic microorganisms were isolated in 2/188 (1%) patients.

The importance of adequate dosing of tedizolid was highlighted in a study that evaluated the production of phenol-soluble modulins by *S. aureus* strains from skin and soft tissue infections at different concentrations of the antibiotic.[71] Tedizolid inhibited the production of these proteins at half the MIC concentration, mainly affecting the production of phenol-soluble modulin alpha 3 and, to a lesser extent, the production of phenol-soluble modulin alpha 4. However, when the concentration of tedizolid was one-quarter and one-eighth of the MIC, it induced the production of phenol-soluble modulins, mainly in those strains with a low baseline production of phenol-soluble modulin alpha 3. The highest increase observed in the phenol-soluble modulin alpha 3 concentration was 4.6 from 2.5 mcg/mL. Similar results were obtained with the control strain, increasing the phenol-soluble modulin alpha 3 concentration from 3.90 to 5.43 and 5.63 mcg/mL with tedizolid concentrations at one-quarter and one-eighth of the MIC value, respectively. This study highlights the importance of the adequate dosing of these antibiotics with an aim to minimize the potential for induction of virulence.

A Phase III randomized double-blind multicenter study was carried out to evaluate the efficacy of tedizolid phosphate 200 mg daily taken orally for 6 days compared with linezolid 600 mg every 12 hours taken orally for 10 days in 667 patients with acute bacterial skin and soft tissue infections from North America, South America, and Europe.[72] Tedizolid was not inferior to linezolid when the primary and secondary endpoints were evaluated in the intent-to-treat analysis.[73] Given that the duration of tedizolid treatment was 4 days fewer than that of linezolid, an additional analysis to the previous study was conducted in the 245 patients who were diagnosed with cellulitis with a minimum total surface area of the lesion of 75 cm^2.[74] The US Food and Drug Administration (FDA) endpoint was cessation of lesion extension and absence of fever at 48–72 hours, while the European Medicines Agency (EMA) endpoint was evaluation of the clinical result by the investigator 7–14 days after the end of treatment, both in the intent-to-treat group. The FDA endpoint was obtained in 72% (53/74) of the patients in the USA and in 82% (37/45) of the patients in Europe who received treatment with tedizolid, whereas, in the case of linezolid, these values were 69% (55/80) and 76% (35/46), respectively. Similarly, the EMA endpoint was obtained in 82% (61/74) of the patients in the USA and in 98% (44/45) of the patients in Europe who received treatment with tedizolid, whereas, in the case of linezolid, these values were 78% (62/80) and 91% (42/46), respectively. According to the results, the cure rate was higher in US and European patients who received tedizolid, for both the FDA and EMA endpoints.

A second Phase III randomized double-blind multicenter study is currently underway with the same objective as the

previous study, but is evaluating the transition from IV to oral route with both tedizolid phosphate and linezolid.[75]

Tolerability

Based on the adverse effects described for linezolid, several studies have been conducted with tedizolid to ascertain whether this molecule improves the toxicity profile of linezolid.

In general, the tolerability of tedizolid phosphate has been evaluated in several studies.[40,76,77] One of them was performed in 40 healthy subjects who received either single doses of the antibiotic ranging from 200 to 1200 mg or placebo.[76] Twenty-eight treatment-related adverse effects, all of mild severity and apparently independent of the dose, were reported, including nausea (10%), dizziness (6.7%), diarrhea (6.7%), and nasal congestion (6.7%).

In a second study with ten adolescent subjects aged between 12 and 17 years, no serious adverse effects were observed, nor were there alterations in the electrocardiogram or analytical parameters after the administration of a single dose of 200 mg tedizolid phosphate.[77] Only one patient presented with mild abdominal pain related to the tedizolid phosphate treatment.

Another study evaluated the tolerability and safety of tedizolid treatment at doses of 200, 300, and 400 mg administered during a 5–7 day period in 188 adult patients with skin and soft tissue infections.[40] Adverse effects were reported in 69.1% of the patients, of which 24.6% were classified as moderate and 72.3% as mild; treatment did not have to be interrupted in any case (Table 8). Only 2.7% of the patients experienced serious adverse effects, none of which was attributable to the drug. None of the toxicities was dose-dependent. The adverse effects reported by the investigators as treatment-related included nausea (16.5%), diarrhea (8.5%; *Clostridium difficile* was not isolated in any case), vomiting (6.9%), and headache (6.4%). One patient experienced an increase in their QT interval of more than 60 ms.

The tolerability of tedizolid in IV infusion was evaluated in ten healthy patients who received an infusion of tedizolid phosphate 200 mg in 250 mL of saline solution for 60 minutes by peripheral vein for 3 days.[78] Each patient acted as their own control by receiving placebo in the other treatment arm. Phlebitis was evaluated using the Visual Infusion Phlebitis (VIP) scale and good peripheral tolerance was demonstrated.

Currently, several studies evaluating the safety profile of tedizolid are underway. One of these is a Phase II open-label multicenter clinical trial evaluating the tolerability of the administration of 200 mg of tedizolid phosphate once daily in patients over 18 years of age with skin infections (major cutaneous abscesses, erysipelas, and cellulitis).[79]

Table 8 Most common treatment-emergent adverse events (>2% of treated subjects) (N = 188)[40]

Adverse effect(s)	N (%)
Any adverse effect	130 (69.1)
Cardiac disorders	4 (2.1)
Tachycardia	4 (2.1)
Gastrointestinal disorders	71 (37.8)
Diarrhea	16 (8.5)
Dry mouth	4 (2.1)
Nausea	35 (18.6)
Vomiting	19 (10.1)
General disorders and administration site conditions	15 (8.0)
Fatigue	5 (2.7)
Pain	6 (3.2)
Infections	41 (21.8)
Abscesses	22 (11.7)
Cellulitis	4 (2.1)
Skin infections	8 (4.3)
Investigations	8 (4.3)
Increase in blood pressure	7 (3.7)
Metabolism and nutrition disorders	6 (3.2)
Decreased appetite	5 (2.7)
Central nervous system disorders	30 (16.0)
Dizziness	5 (2.7)
Headache	21 (11.2)
Psychiatric disorders	16 (8.5)
Insomnia	6 (3.2)
Respiratory disorders	15 (8.0)
Flu	5 (2.7)
Oropharyngeal pain	4 (2.1)
Rhinorrhea	4 (2.1)
Skin and subcutaneous tissue disorders	21 (11.2)
Pruritus	4 (2.1)
Rash	5 (2.7)
Skin lesions	7 (3.7)

In general, the tolerability of tedizolid phosphate is similar to that observed with linezolid, according to a Phase III study that compared the safety profile of the adverse effects of treatment with tedizolid phosphate 200 mg once daily for 6 days or linezolid 600 mg twice daily for 10 days in patients with skin and soft tissue infections.[73] The results showed a drug-related adverse effects rate of 24.2% in the group that received tedizolid phosphate compared with 31.0% in the group that received linezolid.

One of the greatest concerns with linezolid treatment is the potential for developing blood toxicity, including anemia, thrombocytopenia, leucopenia, or pancytopenia; an association with the duration of antibiotic treatment has been observed.[80,81] Therefore, weekly complete blood counts are recommended, especially in patients who present with prior myelosuppression or who receive concomitant myelotoxic

drugs,[82] and treatment should be discontinued in patients who develop this adverse effect. Myelosuppression associated with linezolid is one of the main factors that limit its use.

Thus, of great therapeutic advantage would be the development of new molecules belonging to the oxazolidinone family that maintain antimicrobial activity but have a lower hematological toxicity profile. As such, the objective of several studies has been to evaluate the hematological toxicity of tedizolid phosphate. One study conducted in animals monitored signs of toxicity after the administration of increasing single doses up to 250 mg/kg IV and 2000 mg/kg orally in rats and mice of both sexes.[83] The toxic effects of administration of tedizolid phosphate at doses between 10 and 100 mg/kg for 4 weeks were also evaluated. The median lethal dose ranged from 244 and 274 mg/kg for the IV route and 2000 and 2052 mg/kg for the oral route.

The repeat-dose no observed adverse effect level was 30 mg/kg for males and 10 mg/kg for females and the toxicity target organs were both the lymphatic and hematopoietic organs, such as the spinal cord, thymus, spleen, and lymph nodes.

A Phase I controlled study with linezolid 600 mg twice daily and placebo evaluated the hematological toxicity of tedizolid phosphate at doses of 200, 300, and 400 mg once daily administered for 21 days in 40 healthy subjects.[84] No hematological adverse effects or clinically meaningful changes in blood cell counts were reported with 200 mg once-daily administration for 21 days. However, hematological changes increased with dose and duration of administration such that the administration of 400 mg once daily of tedizolid phosphate resulted in hematological alterations starting during the second week of treatment. These alterations were similar to those observed with linezolid 600 mg twice daily, and occurred at approximately the same time. In another study by the same authors, treatment discontinuation was reported in two patients who received 400 mg of tedizolid phosphate due to a decrease in reticulocyte count in one case and in white cell count in the other, and linezolid treatment discontinuation in one patient due to a decrease in reticulocyte count.[85] Thus, only a few hematological adverse effects have been observed for tedizolid phosphate at a dose of 400 mg used for more than 2 weeks. However, given that the clinical and microbiological efficacy is similar for the 200, 300, and 400 mg doses,[55] the administration of lower doses could be considered to reduce the potential for developing myelosuppression.

Additionally, isolated cases of optic neuritis have been reported in patients treated with linezolid, who have had to discontinue treatment.[86,87] Although the mechanism causing this is not entirely clear, a mechanism similar to that of optic neuropathy due to nutritional deficiency has been proposed.[88] Currently, a Phase I clinical trial is under way to evaluate the neurological and ophthalmologic safety of the oral administration of 200 mg of tedizolid phosphate once daily for 10 days in healthy adults aged between 18 and 65 years.[89]

Drug interactions

Tedizolid does not inhibit the monoamine oxidase (MAO) system in vivo, due to greater antibiotic potency relative to MAO inhibition. This gives it an advantage over linezolid, which exercises a weak, reversible, and nonselective inhibition of MAO that can trigger potential interactions with adrenergic and serotonergic drugs. Therefore, it improves the profile of possible interactions with serotonin reuptake inhibitors and other compounds with serotonergic activity, as well as adrenergic agents, dietary tyramine, and endogenous biogenic amines with the consequent negative effects on the central nervous system and blood pressure.[90,91]

Two randomized double-blind placebo-controlled crossover Phase I studies have been completed evaluating the potential for tedizolid phosphate to inhibit MAO.[92] A comparison of the effects on systolic blood pressure (SBP) of the concomitant administration of tedizolid phosphate and pseudoephedrine against the administration of the antibiotic with placebo was investigated in 18 healthy subjects. No differences were observed in median maximum SBP change from baseline for pseudoephedrine treatment with tedizolid phosphate or placebo, and the number of subjects with SBP increases of 15 mmHg or higher were similar between groups (four with tedizolid phosphate and five with placebo).

Similarly, a trial in healthy adults evaluated the dose of tyramine needed to cause a 30 mmHg increase in SBP (TYR_{30}) in combination with 200 mg tedizolid phosphate once daily or with placebo. Modest increases in sensitivity to tyramine were observed with tedizolid phosphate relative to placebo, but the TYR_{30} with tedizolid (339 mg) was only 28% lower that the TYR_{30} with placebo and was high enough to mean that adverse vascular effects due to intake of food with a high tyramine content are unlikely.

The potential for serotonin syndrome, a potentially fatal consequence of MAO inhibitor compounds, was evaluated in a mouse head-twitch model[92] showing that tedizolid was comparable to placebo (vehicle) in its potential to induce head twitches, an established marker of serotonergic activity. In contrast, linezolid induced a head-twitch response comparable to fluoxetine, a compound known to increase serotonin concentrations by blocking reuptake.

Stability and compatibility

The prodrug demonstrated water solubility greater than 50 mg/mL and excellent chemical stability, remaining unaltered after 8 hours in solutions with different pH, including a glycosylated saline solution with a practically neutral pH of 6.47.[31] The physicochemical properties of the prodrug resolve the water solubility problems observed during the development of other molecules, such as DA-7867, whose reduced water solubility and bioavailability by the oral administration route limited its use, despite its high antimicrobial activity.[93] The compatibility of tedizolid phosphate has not been the object of any study to date; however, the dose of the drug was administered diluted in 250 mL of saline solution in two studies in healthy adults.[33,78]

Conclusion

The emergence of ABSSSI with microorganisms resistant to current treatment options indicates a need to expand the available therapeutic arsenal. Tedizolid phosphate showed favorable results in the treatment ABSSSI in the first Phase III clinical trial. Tedizolid has more potent in vitro activity than linezolid against strains of *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp., including strains resistant to linezolid and strains with reduced susceptibility to vancomycin or daptomycin. Moreover, tedizolid phosphate shows favorable pharmacokinetic and safety profiles that, along with a reduced potential for drug interactions, make this molecule an attractive option in circumstances in which the activity of currently available agents is limited.

Disclosure

The authors declare no conflicts of interest in this work.

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