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REVIEW ARTICLE

Pharmacokinetics and Pharmacodynamics of Tedizolid

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Abstract

Tedizolid is an oxazolidinone antibiotic with high potency against Gram-positive bacteria and currently prescribed in bacterial skin and skin-structure infections. The aim of the review was to summarize and critically review the key pharmacokinetic and pharmacodynamic aspects of tedizolid. Tedizolid displays linear pharmacokinetics with good tissue penetration. In in vitro susceptibility studies, tedizolid exhibits activity against the majority of Gram-positive bacteria (minimal inhibitory concentration [MIC] of ≤ 0.5 mg/L), is four-fold more potent than linezolid, and has the potential to treat pathogens being less susceptible to linezolid. Area under the unbound concentration–time curve (*f*AUC) related to MIC (*f*AUC/MIC) was best correlated with efficacy. In neutropenic mice, *f*AUC/MIC of ~ 50 and ~ 20 induced bacteriostasis in thigh and pulmonary infection models, respectively, at 24 h. The presence of granulocytes augmented its antibacterial effect. Hence, tedizolid is currently not recommended for immunocompromised patients. Clinical investigations with daily doses of 200 mg for 6 days showed non-inferiority to twice-daily dosing of linezolid 600 mg for 10 days in patients with acute bacterial skin and skin-structure infections. In addition to its use in skin and skin-structure infections, the high pulmonary penetration makes it an attractive option for respiratory infections including *Mycobacterium tuberculosis*. Resistance against tedizolid is rare yet effective antimicrobial surveillance and defining pharmacokinetic/pharmacodynamic targets for resistance suppression are needed to guide dosing strategies to suppress resistance development.

Key Points

Tedizolid is a clinically useful antibiotic with activity against Gram-positive bacteria including methicillin-resistant *Staphylococci* and vancomycin-resistant *Enterococci* and currently recommended for patients with skin and skin-structure infections.

The pharmacokinetic (high bioavailability, once-daily dosing, and lack of dosing adjustment in special patient populations) and safety profile as well as high tissue penetration make it a potential candidate for pulmonary infections.

Further research is needed to optimize its existing usage, explore new therapeutic indications beyond skin and skin-structure infections, and to prevent resistance development.

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1 Introduction

With the increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), and the emergence of vancomycin (VAN) less susceptible isolates, the first-line therapy options are shrinking to treat these serious infections [1]. Linezolid (LNZ), an oxazolidinone, was the first in this new class of antimicrobials to be effective against MRSA and less susceptible VAN isolates and widely used as an alternative to treat Gram-positive infection [2, 3]. However, twice-daily dosing, its hematological side effects (thrombocytopenia and myelosuppression), and the emergence of drug resistance, particularly the horizontally transferrable *cfr*-resistant genes, limit its clinical utility. Tedizolid (TDZ) [formerly called torezolid, TR-700, or DA-7157] is a new oxazolidinone antibiotic with a more favorable pharmacokinetic (PK) and safety profile compared with LZD. It also displayed enhanced antimicrobial activity mainly against Gram-positive bacteria compared with LZD and is currently approved for use in skin and skin-structure infections. In this review, we aim to critically summarize and review the key preclinical and clinical PK and pharmacodynamic (PD) aspects of TDZ as well as identify further directions of research.

2 Methods

A systematic literature search was conducted using terms "tedizolid," "tedizolid phosphate," "torezolid," "TR 700," and "DA-7157" with or without terms "pharmacokinetics" or "PK" and/or "pharmacodynamics" or "PD" or "resistance" or "immune modulation" or "mycobacterium tuberculosis" or "TB" on PubMed and Web of Science. Original research articles were selected till August 2021.

3 Pharmacokinetics

The pharmacokinetics of TDZ was studied in both healthy subjects and patients. Because of poor water solubility, TDZ is administered as TDZ phosphate, which is rapidly hydrolyzed by plasma phosphatases into the free active moiety TDZ.

3.1 PK Profile in Healthy Subjects

With both oral or intravenous (IV) dosing, TDZ shows a volume of distribution of ~100 L and displays an elimination half-life of ~11 hours, approximately two-fold higher than LNZ, allowing for once-daily administration of TDZ in comparison to the twice-daily dosing of LNZ. Because of the high bioavailability (~91%), no dose adjustment is required while switching between both administration routes. At a dose range from 200 to 1200 mg/day, the area under the concentration–time curve from zero to infinity ($AUC_{0-\infty}$) ranges from 21.6 to 123.1 mg•h/L while the maximum concentration (C_{max}) ranges from 1.8 to 9.5 mg/L. For the standard human dose of 200 mg/day, the C_{max} and $AUC_{0-\infty}$ are ~1.8–2.6 mg/L and ~21.6–32.7 mg•h/L, respectively [4]. After multiple doses of IV 200 mg , at day 7, the area under the concentration–time curve from 0 to 24 hours (AUC_{0-24h} was higher (29.2 mg•h/L) compared with day 1 (22.3 mg•h/L) [5]. At 200 mg/day, the clearance (CL) values range from 5.9 to 6.5 L/h. The pharmacokinetics was found to be linear in the dose range of 100–600 mg/day [4–7]. Food had no effect on the area under the concentration–time curve from 0 to 72 h (AUC_{0-72}), but delayed C_{max} by 26% [4]. Reported plasma protein binding ranges from 70 to 90% [8]. Tedizolid is predominantly excreted via the feces (~69%) as an inactive sulfate metabolite while ~10% is excreted via urine [9].

A two-compartment model with sigmoidal absorption and linear elimination was developed that successfully described the plasma disposition kinetics when applied to the pooled data from seven clinical studies (phase I–III) [10]. Neither a clinically important covariate nor ethnic differences affected the PK disposition significantly [11–14]. The PK characteristics are shown in Table 1.

3.2 Pharmacokinetics in Special Patient Populations

3.2.1 Renal and Hepatic Impairment

Two single-dose (200 mg), phase I, parallel-group studies in patients with renal and hepatic impairment showed no appreciable difference in PK parameters when compared to the control groups. In subjects with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2), the mean AUC_{0-72} (32.02 vs 29.69 mg•h/L), C_{max} (3.11 vs 3.12 mg/L), CL (5.68 vs 6.13 L/h), and half-lives (12.25 vs 12.85 hours) were indifferent to the respective control [15]. In patients undergoing intermittent hemodialysis, a minor impact on CL (< 10%) was reported [15, 16]. In in vitro models of continuous renal replacement therapy, transmembrane clearance of TDZ depended on hemodialysis type, ultrafiltrate rate, and blood flow rate. However, no need for dose adjustment in clinical settings was concluded [17]. However, substantial changes in protein binding, as they might occur in severe hepatic impairment or also in critically ill patients, might increase the CL of TDZ and warrants further investigation.

In patients with moderate and severe hepatic impairment, the CL values were 6.06 and 5.22 L/h while the area under the concentration–time curve from 0 to 96 hours was 29.89 and 34.80 mg•h/L, which was 22% and 34% higher than the control group (22.80 and 24.37 mg•h/L), respectively. However, this increased exposure is likely clinically irrelevant and was well tolerated in other multiple-dose clinical studies and hence necessitates no dose adjustment [6, 15].

3.3 Elderly Individuals, Adolescents, and Children

Tedizolid depicted similar PK disposition kinetics after IV/oral administration of 200 mg/day in elderly individuals, adolescents, and adults. The AUC_{0-24} values for adolescents (25.5 mg•h/L) were within the range of the previously reported adult values (~30 mg•h/L). Mean C_{max} was similar after oral administration, but was 43% higher than adults after an IV infusion (3.66 mg/L compared with ~2.5 mg/L), suggesting a 200-mg daily dose can be further studied in adolescents [18]. In children aged 2–12 years, once-daily doses of 3–6 mg/kg provided a comparable exposure ($AUC_{0-\infty}$: 17.2–29.6 mg•h/L) to that reported for adults and adolescents. However, in children (aged 2–6 years), the C_{max} was higher than in adults (4.19 vs ~2.5 mg/L), which hints

Table 1 Pharmacokinetic parameters of tedizolid at a therapeutic dosage (200 mg/day)

Population	Author (year), study type	AUC[a] (mg• h/L)	Clearance (L/h)	V_d (L)[a]	C_{max} (mg/L)[a]	Half-life (hours)
Healthy subjects	Flanagan-I et al. (2014) [5], food effect and relative bioavailability	Single dose: 25.4 ± 4.6	6.08 ± 1.08	95.7 ± 23.5	2.0 ± 0.4	~11 for all dose groups
		Multiple doses: 21.6 ± 6.5	7.48 ± 2.12	117 ± 21.9	1.8 ± 1.2	
Healthy subjects	Flanagan-II et al. (2014) [4], single IV dose or crossover IV and oral	Single dose (IV)[a], 32.6 ± 8.3	5.4 ± 1.8	67.1 ± 15.3	2.6 ± 0.6	11 ± 0.8
		IV: 29 ± 6.1 Oral: 26.7 ± 6.0	IV: 5.9 ± 1.5 Oral: 6.5 ± 1.9	IV: 71.5 ± 12.7 Oral: 100.1 ± 17.7	IV: 2.5 ± 0.4 Oral: 1.9 ± 0.4	IV: 11.4 ± 2.0 Oral: 11.1 ± 2.1
Renal or hepatically impaired subjects	Flanagan-III et al. (2014) [15], single dose, IV or oral	Renal (severe, predialysis infusion, post-dialysis): 29.99 ± 8.97, 23.15 ± 8.10, 21.01 ± 4.71	–	–	3.12 ± 0.85, 2.53 ± 0.95, 2.86 ± 1.01	12.85 ± 2.28, 11.41 ± 1.78, 11.73 ± 2.33
		Hepatic (moderate, severe): 30.47 ± 17.50, 35.23 ± 21.13	–	–	2.08 ± 0.74, 2.20 ± 0.80	14.94 ± 3.49, 14.19 ± 2.92
Adolescents	Bradley et al. (2016) [18], IV infusion or oral dose	Oral: 25.2 ± 9.2	7.19 ± 2.12	83.5 ± 28.2	2.23 ± 0.5	8.26 ± 1.99
		IV: 27.8 ± 7.3	6.31 ± 1.81	59.3± 12.2	3.85 ± 1.51	6.64 ± 0.69
Obese vs nonobese subjects	Flanagan et al. (2017) [21]	Oral: (obese, nonobese) 25.4, 28.5	–	–	–	–
		IV: (obese, nonobese) 25.4, 28.7	–	–	–	–
Elderly subjects	Flanagan et al. (2018) [20], single oral dose	Elderly: 34.7 ± 10.6	5.2 ± 1.6	91.6 ± 28.2	2.6 ± 0.7	12.3 ± 1.3
		Adults: 29.9 ± 5.9	5.7 ± 1.3	96.6 ± 21.0	2.4 ± 0.5	11.8 ± 1.0
Subjects with cystic fibrosis	Park et al. (2018) [25], IV infusion or oral dose	$AUC_{0–24}$: IV: 20.7 ± 3.92	9.72	88	2.92 ± 0.624	-
		$AUC_{0–24}$: oral: 22.1 ± 5.72			2.22 ± 0.745	-
Subjects with diabetic foot infections	Stainton et al. (2018) [28], patients vs healthy volunteers, oral dose	Patients $AUC_{0–24}$: 18.5 ± 9.7	15.0 ± 6.8	177.3 ± 53.7	1.5 ± 0.5	9.1 ± 3.6
		Healthy adults $AUC_{0–24}$: 28.7 ± 9.6	11.4 ± 3.3	143.4 ± 50.4	2.7 ± 1.1	8.9 ± 2.2

$AUC_{0–\infty}$ AUC from zero to infinity, *$AUC_{0–24}$ AUC* from 0 to 24 hours, *C_{max}* maximum concentration, *IV* intravenous, *SD* standard deviation from the mean, *V_d* volume of distribution

[a]AUC = area under the concentration–time curve

Data from [4, 5, 15, 18, 20, 21, 25, 28]

to the splitting of doses as an alternative option [19]. The small sample size ($n = 6$) of the study indicates that further research might be needed to position TDZ for clinical use in children. Tedizolid displayed similar PK characteristics (200-mg single dose) in elderly subjects when compared to the adult population ($AUC_{0–72}$ of 34.7 vs 29.9 mg•h/L) and hence no dose adjustment seems necessary in this patient collective [20].

3.4 Obese Population

In obese patients, both IV and oral administration of the standard 200-mg daily dose, the $AUC_{0–\infty}$, and C_{max} geometric mean ratios were 11–18% lower compared with healthy control subjects, indicating no significant difference between both populations [21, 22]. Similarly, no disparity in PK profiles was noted in morbidly obese patients compared to the nonobese subjects [23]. There were no significant

differences in PK profiles of patients after bariatric surgery compared to the adult population [24].

3.4.1 Cystic Fibrosis

The CL (mean total and distributional CLs of 9.72 and 4.13 L/h, respectively) was higher in patients with cystic fibrosis compared with values reported earlier (6.69 and 0.959 L/h, respectively) for healthy volunteers and patients with complicated skin and skin-structure infections (pooled data) in one study, but are almost similar to the CL values in patients with skin and skin-structure infections (8.28 and 2.95 L/h, respectively) [25]. Whether these changes in CL (in total or in parts) are due to PK alterations in cystic fibrosis or pathophysiological changes during infection necessitates further investigations to guide an optimal dosing strategy in patients with cystic fibrosis.

3.4.2 Drug Interactions

Although TDZ shows in vitro a weak reversible inhibition of monoamine oxidases, provocative testing of a potential interaction between the therapeutic dose of TDZ and oral pseudoephedrine or tyramine in healthy volunteers in two randomized placebo-controlled trials exhibited no potential serotonergic or hypertensive adverse effects. The results were in line with the murine model studied with a similar objective [26]. Nonetheless, patients treated with TDZ and monoamine oxidases inhibitors should be carefully monitored for potential side effects.

3.4.3 Target Site Exposure

Tedizolid exhibits high tissue penetration into both skin and pulmonary tissues. When investigated in skin and adipose tissue using microdialysis in healthy subjects after a single oral dose of 600 mg, the penetration ratio (measured as free area under the unbound concentration–time curve [*f*AUC]/minimal inhibitory concentration [MIC]) $fAUC_{tissue}/fAUC_{plasma}$) for adipose and muscle tissue were 1.1 ± 0.2 and 1.2 ± 0.2, respectively [27], suggesting that unbound plasma represents a reasonable surrogate for tissue concentrations. Similarly, in another microdialysis study in patients with diabetic foot infection receiving 200 mg daily for 3 days, tissue concentrations approximated unbound plasma concentrations: the unbound tissue/unbound plasma concentration ratio was 1.1 (range 0.3–1.6) for patients with diabetic foot infection and 0.8 (range 0.7–1.0) for healthy volunteers, respectively [28]. At a daily dose of 200 mg orally for 3 days in healthy adults, in comparison to the $fAUC_{0–24}$ in plasma and assuming negligible protein binding in epithelial lining fluid (ELF), TDZ penetration ratios were approximately 40-fold higher in ELF and 20-fold higher in alveolar macrophages compared with plasma. The $fAUC_{0–24}$ values for ELF and alveolar macrophages were 109.3 and 52.95 mg•h/L, respectively. This high pulmonary penetration advocates for the potential role of TDZ in the treatment of pulmonary infections [29]. Whether this increased penetration is due to active transport or any other mechanism is still unknown and needs further investigations. Moreover, TDZ shows good sputum penetration with a sputum-to-plasma ratio of 2.88 in patients with cystic fibrosis [30]. Tedizolid-induced suppression of mucin production in alveolar membranes could also contribute to the higher pulmonary penetration of TDZ [31]. Although varying degrees of unbound cerebrospinal fluid-to-unbound plasma penetration ratios are reported in the literature for humans and rats, further studies are needed to confirm these findings to define the potential role of TDZ to treat central nervous system infections [32, 33]. A summary of the tissue penetration of TDZ and LNZ is provided in Table 2.

4 Pharmacodynamics

4.1 Antimicrobial Spectrum

The antimicrobial spectrum of TDZ covers clinically relevant Gram-positive bacteria including methicillin-susceptible *Staphylococcus aureus* (MSSA), MRSA, methicillin-susceptible *S. epidermidis*, methicillin-resistant *S. epidermidis*, VAN-sensitive and VAN-resistant enterococci (VRE), penicillin-susceptible *Streptococcus pneumoniae* (PSSP) and penicillin-resistant *S. pneumoniae* (PRSP), and other frequently reported cutaneous and respiratory pathogens (Table 3) [2, 34]. Most Gram-positive bacteria mentioned above are susceptible to TDZ with MIC values of ≤ 0.5 mg/L [35–39]. However, TDZ, compared with Gram-positive bacteria, exhibits lower potencies against Gram-negative bacteria such as *Hemophilus influenzae* (16 mg/L) and *Moraxella catarrhalis* (4 mg/L) [35, 40]. Like LNZ, TDZ binds to the ribosomal RNA 50S subunit and inhibits protein synthesis [2].

Staphylococcus aureus is a frequently reported pathogen in many skin, soft-tissue, and respiratory tract infections for which many commonly used antimicrobials gradually lost efficacy, resulting in an increasing number of MRSA, VAN-resistant, and LNZ-resistant isolates [41, 42] and often limiting the available treatment choices of antimicrobials in the underlying infections. Multiple comparative studies repeatedly demonstrated at least a four-fold higher potency of TDZ compared with LNZ. Moreover, TDZ shows efficacy against VAN-resistant, daptomycin (DAP)-resistant, and some LNZ-resistant isolates and hence provides an alternative option to treat the less susceptible isolates of these antimicrobials [35, 37, 43–45]. Other studies with further Gram-positive isolates mentioned earlier have almost similar findings [11, 34, 35, 38, 40, 43, 46–53]. However, few isolates that were

Table 2 Tissue penetration (unbound tissue/unbound plasma) of tedizolid (TDZ) vs linezolid (LNZ)

Tissue	TDZ	LNZ
Adipose	1.1 [27]	1.4 [138]
Muscle	1.2 [27]	1.3 [138]
Lungs	40 [29]	~ 1.0 [140]
CNS	0.5 [32]	0.6–1.6[a] [141, 142]
Bones	–	1.09 [143]

CNS central nervous system

[a]Total cerebrospinal fluid/total plasma

LNZ resistant (plasmid borne *cfr* multidrug resistance gene) showed a lower susceptibility (MIC > 0.5 mg/L) [54–59]. Hence, isolates above the MIC threshold of >0.5 mg/L are less likely to be successfully treatable with TDZ [10]. A susceptibility breakpoint of 0.5 mg/L is recommended by EUCAST for *Staphylococcus* species, *Streptococci* (A, B, C, G) and viridians (*Streptococcus anginosus*) [60]. The results from the Surveillance of Tedizolid Activity and Resistance Program (STAR program) in Europe showed that the majority of the *Enterococci* exhibit MIC values of < 0.5 mg/L for TDZ and support the EUCAST breakpoint for *Staphylococci* [36, 61–64]. A recent PK/PD simulation-based analysis on existing PK and PD data from the literature reported a similar PK/PD breakpoint of 0.5 mg/L for the majority of Gram-positive isolates [65]. However, no EUCAST susceptibility breakpoints are yet established for *Enterococci* [60].

With high penetration into human macrophages (TPH-1), TDZ showed good intracellular efficacy against *Listeria monocytogenes* (MIC 0.125 mg/L) and *S. aureus* (MIC 0.25–1 mg/L) in infected TPH-1 cells. The intracellular penetration can be potentially exploited to treat intracellular pathogens [66]. Its moderate activity against anaerobes particularly against *Bacteroides fragilis* (MIC_{90} of 1 mg/L) can be exploited to treat mixed aerobic and anaerobic infection [67]. Tedizolid expresses good activity against several clinically relevant respiratory pathogens such as PRSP (MIC_{90} of 0.25 mg/L) and PSSP (MIC_{90} of 0.125–0.25 mg/L) and has a clinical potential to treat respiratory infections [12, 35, 49, 68].

4.2 In Vitro Pre-Clinical Studies

In vitro time-kill studies depict bacteriostatic activity for TDZ in most Gram-positive isolates. When studied against MRSA (MIC = 0.5 mg/L), methicillin-resistant *S.*

Table 3 Summary of the pharmacodynamics of tedizolid

Antimicrobial activity	
Gram-positive [35, 36, 144–146]	
Staphylococcus aureus (MRSA, MSSA), *Staphylococcus epidermidis* (including methicillin-resistant isolates)	MIC_{90}: 0.25 mg/L
Enterococci:	
Enterococcus faecium, Enterococcus faecalis including VRE	MIC_{90}: 0.25–0.5 mg/L
E. faecalis (linezolid non-susceptible)	MIC_{90}: 1.0[a] mg/L
Streptococcus pneumoniae (including penicillin-resistant isolates, β-hemolytic streptococci and viridians group)	MIC_{90}: 0.25 mg/L
Anaerobes	
(peptostreptococci sp., *Clostridium difficile*)	MIC_{90}: 0.25 mg/L
Gram-negative anaerobes	MIC_{90}: 1.0[a] mg/L
Bacteroides sp., **Mycobacteria** [129, 147]	
Mycobacterium abscessus sp.	MIC_{90}: 8.0[a] mg/L
Mycobacterium tuberculosis	MIC_{90}: 0.5 mg/L
Clinical summary	
Approved indication [90, 91, 98, 99]	Dose: 200 mg/day for 6 days (both oral and IV)
Acute bacterial skin and skin-structure infections	
Potential applications	
Bacterial pneumonia (HAP and VAP associated with MSSA and MRSA)	
Adverse effects	
GIT: nausea, vomiting, diarrhea, and dyspepsia	
Myelosuppression: thrombocytopenia and anemia	
Neurological: peripheral neuropathy	
Others: headache	

GIT gastrointestinal tract, *HAP* hospital-acquired pneumonia, *IV* intravenous, *MIC_{90}* Minimum inhibitory concentration against 90% of the isolates, *MRSA* methicillin-resistant *S. aureus, MSSA* methicillin-susceptible *S. aureus*, *VAP* ventilator-associated pneumonia, *VRE* vancomycin-resistant *Enterococcus*

[a]Above EUCAST susceptibility breakpoint for *Staphylococcus* species, *Streptococci* (A, B, C, G) and viridians

epidermidis (MIC = 0.25 mg/L) and *Enterococcus faecalis* (MIC = 0.25 mg/L) a bacteriostatic effect was observed at both MIC and 16× MIC for all strains while a bactericidal activity (3 log-kill at 24 hours) at 16× MIC was observed for *S. pneumoniae* (MIC = 0.25 mg/L) [68]. In line with the above results, a bacteriostatic effect of TDZ was observed against VRE *E. faecium* (MIC 1 mg/L) and *E. faecalis* (0.25 mg/L) after 24 hours at 2× MIC [69]. In another time kill study, TDZ exhibited bacteriostatic activity against MRSA and MSSA, while regrowth was observed with LNZ treatment at the MIC and 2× MIC after 24 hours (LNZ MIC: 1 and 2 mg/L for MRSA and MSSA, respectively) [70].

Tedizolid was also evaluated in combination. In a static time kill study using a concentration equal to 0.5× MIC of the respective isolate against MRSA (MIC, 0.25–0.5 mg/L) and *S. epidermidis* (MIC, 0.125–1 mg/L), TDZ showed synergistic (≥ 2 $\log_{10}$ CFU/mL reduction in combination vs most active single agent) activity with rifampicin and doxycycline, while, in contrast, an antagonistic (≥ 1 $\log_{10}$ CFU/mL growth) activity of TDZ and moxifloxacin (MXF) was observed [71]. However, these findings were not uniform in all the strains ($n = 10$) and warrant further studies. Against *S. aureus* with reduced glycopeptide susceptibility, TDZ alone showed bacteriostatic activity, which was comparable to teicoplanin and rifampicin combination therapy in an in vitro static time kill study [48]. Daptomycin and TDZ while active alone against MRSA, in combination were inferior to the respective monotherapy in an in vitro dynamic model [72]. In an in vitro endocarditis model against VAN-resistant *S. aureus* and VRE (*E. faecium* and *E. faecalis*), a step-down therapy (DAP for 3 days followed by TDZ for 2 days) was as effective as DAP for 5 days [72]. However, no clinical study has yet explored these possible combination therapies.

Overall, TDZ exhibits reasonable bacteriostatic activity against Gram-positive pathogens frequently causative of systemic, skin/cutaneous and respiratory infections, especially *Staphylococci* and *Enterococci*. However, studies demonstrating the antibiotic effect of TDZ for more than 24 hours in static or dynamic in vitro models are limited. Insights from longer concentration–time studies are critical for better understanding its efficacy, dosing strategies, and the pattern and extent of potential resistance development in a full course of therapy.

4.3 In Vivo Preclinical Studies

4.3.1 Murine Infection Models

Several in vivo studies were conducted in localized and systemic murine infection models to evaluate the pharmacokinetics, pharmacodynamics, and the PK/PD parameters best corelated with efficacy of TDZ against a variety of Gram-positive pathogens. The pharmacodynamics of TDZ was evaluated by Louie et al., where a neutropenic thigh infection model with MRSA and MSSA infections was investigated. Tedizolid was equally effective against both MSSA and MRSA while the *f*AUC related to MIC (*f*AUC/MIC) was best correlated with efficacy. The *f*AUC/MIC ratio related with stasis and 1-log kill relative to the starting inoculum was 49.3 and 105.9, respectively, at 24 hours. A mean dose of 37.6 and 66.9 mg/kg of TDZ was required for stasis and 1 log CFU/g, respectively, at 24 h. In comparison, 150 mg/kg of LNZ failed to induce bacteriostasis, demonstrating the higher potency of TDZ as compared with LNZ and hence confirming the in vitro findings in vivo [73].

When evaluated in a systemic infection model (immunosuppressed [IS]) with MSSA and MRSA infection (MIC: 0.125–0.5 mg/L), TDZ demonstrated a 2–9-fold higher activity than LNZ (MIC: 0.5–8 mg/L) with an ED_{50} (dose giving half maximal effect) range of 1.5–3.2 to 4.3–7.6 mg/kg vs 7.7–9.6 to 21.4–29.1 mg/kg of TDZ vs LNZ, respectively [34]. Similarly, in a septicemia model induced by LNZ-resistant MRSA (*cfr* positive), a lower dose of TDZ (20 mg/kg) was superior in activity vs 50 mg/kg of LNZ (100 vs 80% survival). Other studies with *Enterococci* led to similar results [34, 74].

However, in erythromycin-resistant and clindamycin-resistant *Streptococci* in a necrotizing infection murine model, TDZ and LNZ were equally effective [75]. Hence, the higher in vitro potency of TDZ as compared with LNZ seems to translate into the in vivo setting.

4.3.2 Role of Immune System Components

Drusano et al. proposed a critical role of granulocytes in immunocompetent (IC) compared with IS mice in a thigh infection model [76]. Despite similar PK profiles, the TDZ activity in IC mice was approximately 25-fold higher than in IS mice at all studied timepoints (24, 48, and 72 hours). A human equivalent dose of ≤ 200 mg/day vs 2300 mg/day produced stasis (24 hours) in IC and IS mice, respectively, whereas a maximal effect was observed at 200 mg/day in IC mice, suggesting that the efficacy of TDZ is grossly mediated by granulocytes. Based on previous results for IS mice, a *f*AUC/MIC target of 3 was calculated for IC mice for stasis at 24 h as compared with the target of 50 in IS mice [77]. However, when these findings were re-evaluated by Xiao et al. with a similar study design and exposure, contrary to the earlier findings, stasis was achieved in both IC and IS mice after 72 h of TDZ therapy [78]. Moreover, in IS mice, stasis was achieved at 72 h at a lower dose of 166 mg/day compared with the previously reported value (~ 2000 mg/day) by Drusano et al. [78]. The reasons for this discrepancy are unclear. However, based on the findings of

Drusano et al., the current label of TDZ limits its use to IC patients [79]. The *f*AUC/MIC target of 8.9 for stasis at 72 h for MRSA (MIC 0.5 mg/L) in the IS model was close to the clinically reported value of 5–7 in adults [8, 73], and hence correlated well with the human studies [78]. The results also suggest the duration of therapy to be considered (efficacy at 72 h is higher than at 24 h) when comparing the results among murine models. In comparison, in IC mice, a lower target of *f*AUC/MIC <1.3 for stasis was reported for all studied timepoints [79].

Results in a pulmonary infection murine model, with human equivalent pulmonary exposures, with *S. pneumoniae* also showed a less pertinent role of granulocytes in TDZ efficacy [80]. In an IC thigh infection model, both TDZ and LNZ (at human equivalent doses) showed similar activity with *S. aureus* clinical isolate infections [81]. For *Enterococci* (*E. faecalis* and *E. faecium*), in a IC murine model TDZ, despite higher total activity of TDZ than LNZ in vitro, paradoxically, the effect of TDZ was inferior to LNZ in both bacterial killing and relapse prevention at human equivalent dosing [69]. A superior efficacy of LNZ over TDZ contradicts the earlier finding for which a plausible explanation is missing. Keel et al. investigated the role of both infection status and neutropenia and compared PK/PD indices among IC, IS, and noninfected mice at a human equivalent dose of 8.4 mg/kg of TDZ. The $fAUC_{(0-24)}$ was 41% higher in IC and 17% lower in noninfected mice than IS mice. The penetration ratio (bronchoalveolar lavage to blood) was higher for TDZ in infected mice (9.34 and 10.63 for IC and IS) compared with 6.14 in noninfected mice and demonstrates a critical role of infectious status in tissue penetration [82]. A significant decrease of all cytokines (tumor necrosis factor-α, interleukin-1, interleukin-6, and macrophage inflammatory protein-2) was observed at 2 h after the TDZ human equivalent dose as compared with the control in a MRSA-induced pulmonary infection model. Whether this effect was indirectly related to the microbial toxins released by pathogens or induced by TDZ directly remains unclear [83].

An intact immune system is assumed to provide a 2–4 log reduction in AUC/MIC target values [84]; however, the higher granulocyte-mediated effect restricts the clinical utility of TDZ only to IC patients as recommended by the European Medicines Agency [8]. However, the contrasting role of the immune system in some subsequent studies necessitates further investigations to substantiate these findings and define the role of the immune system in relation to TDZ efficacy further. Moreover, PK/PD studies, ideally, covering the full course of therapy, are needed to extend TDZ application in critically ill neutropenic patients where other therapeutic alternatives fail to treat the underlying infection.

4.3.3 Pulmonary Infection Model

While soft-tissue infections are the main therapeutic area for which TDZ is indicated, pulmonary infections represent another major therapeutic area that is frequently investigated and has shown promising potential of clinical application. Choi et al. studied TDZ and LNZ against four PRSP and PSSP in a murine pneumonia model with human equivalent doses. Tedizolid was at least two-fold more potent than LNZ in both PRSP and PSSP systemic infection models, while a lower dose (10 mg/kg/day of TDZ) resulted in a similar outcome (100% survival) as compared to 40 mg/kg/day of LNZ in a PSSP model [85]. In a murine pneumonia model using MRSA and MSSA isolates, the *f*AUC/MIC target related to stasis for both TDZ and LNZ was 19 and 20, respectively, while roughly doubled values (34.6 and 46.1, respectively) were associated with 1-log kill reduction across all strains. These *f*AUC/MIC targets were 2–4-fold lower than the reported values for TDZ and LNZ derived from the thigh infection model [73, 86]. This discrepancy might be explainable by the enrichment of TDZ in ELF [87]. When compared with VAN and LNZ at equivalent human ELF exposure against an IC MRSA pneumonia mouse model, TDZ demonstrated similar efficacy to LNZ but was superior to VAN (100% vs 39% survival) [88, 89]. A similar study supports these findings [83]. In another study, interestingly, pulmonary exposure was almost similar in both IC and IS *S. pneumoniae*-induced pulmonary mice models (~110 mg·h/L) despite unequal dosing (40 mg/kg/day vs 55 mg/kg/day) [80] and further underlines the importance of consideration of target-site drug concentrations when relating systemic exposure to efficacy. These exposures were comparable to humans ELF exposure of 109.30 mg·h/L (200 mg/day), confirming a good correlation of pre-clinical to clinical data. In IS mice, the $fAUC_{0-24}$/MICs associated with stasis and 1-log reduction in pulmonary bacterial burden relative to initial inoculum were 19.21 and 48.29, respectively, which was in line with the findings of Lepak et al. [87]. In total, the above studies highlight good pulmonary penetration and efficacy of TDZ in all studied isolates and provide a rationale to further explore TDZ for treating pulmonary infections.

4.4 In Vivo Clinical Studies

The exposure–response relationship of TDZ was investigated in several single and pooled clinical studies. In patients with complicated skin and skin-structure infections (main pathogen MRSA, MIC_{90}: 0.25 mg/L), Prokocimer et al. reported a dose of 200 mg/day to be as effective as higher doses when administered for 5–6 days. However, an exposure–response relationship was difficult to establish [6]. In the ESTABLISH 1 and 2 clinical trials, 200 mg/day of TDZ was noninferior to 600 mg twice-daily dosing of LNZ in patients

with ABSSSIs and was subsequently licensed for this indication [90, 91]. Moreover, TDZ reduced skin and soft-tissue infection-related hospital admissions in out-patient settings [92]. Based on pooled PK and PD data from four clinical studies (one phase I, one phase II, and two phase III) where doses of 100–400 mg/day were investigated [10, 15, 91, 91, 93, 94], a PK/PD model was developed to relate exposure to efficacy. At a dose of 200 mg/day, the PK/PD index *f*AUC/MIC of 3 was defined to relate to clinical outcomes [77]. The developed PK/PD model relating *f*AUC to MIC was used in a Monte Carlo simulation to predict a therapeutic breakpoint. The *f*AUC/MIC target of 3 results in a probability of target attainment of ~98% at an MIC value of 0.5 mg/L, while for 1 mg/L the probability of target attainment was ~70% and thus deemed not sufficiently high. Therefore, an MIC of 0.5 mg/L was declared the susceptibility breakpoint for TDZ against *S. aureus* (MSSA or MRSA) and can be applied to other common bacterial pathogens having a TDZ MIC of ≤0.5 mg/L [10]. This clinical breakpoint was in line with preclinical studies where at a cut-off value of ≤0.5 mg/L, most Gram-positive isolates were sensitive [95]. In addition to clinical studies in skin and skin-structure infections, in the first phase III clinical study in patients with hospital-acquired and ventilator-associated pneumonia, TDZ (200 mg/day for 6 days) was non-inferior to LNZ (600 mg twice daily for 10 days) in the primary outcome (28 days all-cause mortality). However, the non-inferiority of TDZ to LNZ was not established while comparing the secondary outcome (investigator-assessed clinical response at test of cure) [96]. There are no clear reasons for this discrepancy but the complexity of the disease and the subjectivity of defining "clinical cure" by clinicians can lead to this lack of consistency in the clinical outcomes. This is the first clinical investigation of TDZ in patients with pneumonia and further studies are needed to confirm these findings.

4.4.1 Safety Profile

Tedizolid was generally well tolerated in healthy volunteers as well as in multiple phase II and phase III studies and has a superior safety profile compared with LNZ. When evaluated at a daily dose of 200–400 mg in a phase II study, 69% of the patients reported treatment-emergent adverse drug reactions (ADRs) [72.3% mild; 24.6% moderate] with nausea (18.6%), headache (11.2%), and vomiting (10.1%) most predominant. None discontinued therapy because of TDZ-induced ADRs [6]. In the two phase III trials for licensing (ESTABLISH 1 and 2), TDZ showed a superior safety profile compared with LNZ. Gastrointestinal ADRs (nausea, vomiting, diarrhea, and dyspepsia) were frequently reported (16%), hence expanding the observations of phase II studies [29, 97]. When evaluated in pooled data across completed clinical studies (13 phase I, two phase II, and two phase III), drug-related ADRs were 27% of all participants. In line with previous results, gastrointestinal ADRs (13%) and headache (4%) were predominant [98]. However, none of these trials collected long-term (>3 weeks) safety data. While hematological toxicity is a serious concern during prolonged LNZ therapy, TDZ showed a superior hematological safety profile as compared with LNZ with a lower incidence of thrombocytopenia (platelet counts, < 150,000 cells/mm^3) at days 7–9: among the TDZ treatment group, thrombocytopenia was 3.2% compared with 5.6% in the LNZ treatment arm at standard human doses [99]. When administered for a longer duration (21 days), thrombocytopenia associated with TDZ administration was dose dependent: at a dose of 200 mg/day, no measurable difference in thrombocytes from baseline was observed while at 400 mg/day, up to a 50% decrease was observed in 12.5% of the patients [99, 100]. Further studies with similar findings suggest a lower impact of TDZ on the hematological profile [101]. However, because of the small sample size (n = 40) of the study, the long-term safety of TDZ necessitates further investigations. Studies with slightly longer durations (mean of 27–29 days) support these findings [102–104]. In ESTABLISH 1 and 2 trials, neurological (~ 9%) and dermatological (~6%) toxicities were almost equally often reported for both TDZ and LNZ, which were well supported in other studies [14, 90, 91, 105]. Safety profiles of elderly individuals, adolescents, and children (aged 2–12 years), patients with cystic fibrosis, and renal and hepatically impaired patients were comparable to that of the adult population [15, 19, 20, 25, 106, 107]. The overall safety pattern of TDZ in post-marketing surveillance in the ADR reports (2014–20) in the worldwide US Food and Drug Administration Adverse Events Reporting System was in line with the above results where no serious adverse effect was directly associated with TDZ [108]. For long-term safety, less structured data are available. Yet, in a recent study in patients with bone and joint infections (n = 33) where TDZ was administered for a mean duration of 8 weeks at 200 mg/day, an overall high ADR rate (60%) was reported, and 18% of the patients discontinued the TDZ because of intolerance or severe anemia due to hemorrhage [109]. The results were comparable with overall ADR rates reported in non-tuberculosis mycobacterial infections after an average of 101 days of TDZ administration [110]. A retrospective single-center evaluation of 24 patients with non-tuberculosis mycobacteria infection with an average 7 weeks of standard human doses of TDZ and LNZ showed no differences in hematological safely profiles [111]. Four case reports with long-term use of TDZ in an adolescent patient with pulmonary tuberculosis undergoing a liver transplant (20 months), in a patient with nocardiosis (6 months), in a patient with recurrent MRSA infection (18 months), and in a patient with cutaneous non-tuberculosis mycobacteria infection (8 months) showed no TDZ-induced toxicity [112–115].

Although animal studies illustrated a lack of any neurological change with long-term TDZ administration, long-term neurological safety studies in humans are lacking [116, 117]. The European Medicines Agency, although acknowledging an overall high safety profile for TDZ, indicate myelosuppression and peripheral neuropathy as potential risks associated with TDZ therapy in their risk management plan [118]. A notable increase in the off-label (particularly in terms of treatment duration) use of TDZ necessitates objective evidence to justify its long-term safety [108]. A clinical summary of TDZ is provided in Table 3.

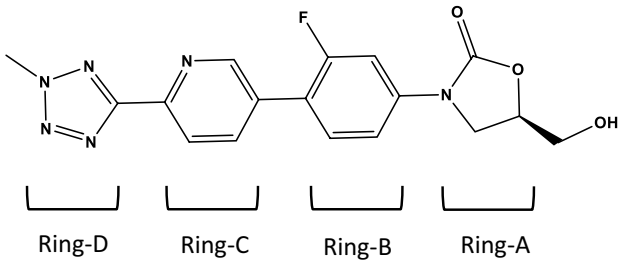

Fig. 1 The chemical structures of tedizolid

5 Resistance to TDZ and PK/PD Targets/ Magnitudes for Resistant Suppression

The main mechanisms of resistance against oxazolidinones comprise chromosomal mutations at the 23S ribosomal rRNA target site, mutations in the rplD gene encoding the 50S ribosomal proteins (L3 and L4) [46, 119], plasmid-born chromosomal mutations (*cfr* methyltransferase gene) [45, 120], and alteration of efflux with ABC transporters (e.g., Opt A) [120, 121]. Because of the presence of a distinct hydroxyethyl group in the molecular structure (Fig. 1), TDZ shows potency against some LNZ-resistant bacteria and stimulates a lower mutation frequency. A comparison of the frequency of resistant mutant selection to TDZ exposed to 2× MIC of *S. aureus* (MRSA and MSSA) was $< 10^{-10}$ to $< 10^{-11}$, respectively, which was approximately two orders of magnitude lower than LNZ ($1–5\times10^{-9}$) [45, 120]. These findings were in line with Jones et al. where a single cell mutation was rare and no growth of *S. aureus* and *E. faecium* was observed at 4×, 6×, and 8× MIC of TDZ [46]. Serial passages of MRSA and MSSA to TDZ with a two-fold increasing exposure (started from 4 mg/L) for 30 days resulted in no elevation in the MIC of MSSA. However, reduced susceptibility of MRSA was observed (0.25 vs 2 mg/L) [120]. Chen et al. reported a majority of the *S. anginosus* group (61.3%) to be non-susceptible to TDZ when the US Food and Drug Administration breakpoint of (≤0.25 mg/L) was applied, which was in contrast to previously reported studies by Prokocimer et al. and Zurenko et al. where *S. anginosus* was sensitive [122–124]. However, the study was conducted in a single center and needs further verification. Enterococcal clinical isolates of *E. faecalis* from China showed ~6–13 % of the studied isolates to be TDZ non-susceptible (MIC ≥0.5 mg/L) [125]. The non-susceptible isolates displayed an abundant plasmid-mediated ABC transporter optrA [50, 121]. Choudhury et al. also reported two clinical isolates (out of 48) of vanA *E. faecium* strains as 'non-susceptible' to TDZ (MIC 1–2 mg/L) [126]. In a recent study, two isolates of *E. faecalis* displayed TDZ MIC values of 2 mg/L (23S rRNA G2576T mutation). Tedizolid exhibited lowered sensitivity (MIC >0.5 mg/L) in LNZ-resistant VRE isolates in Germany [127]. However, further systematic investigations are necessary to establish a correlation between previous LNZ resistance and TDZ susceptibility. In addition to the classical resistance mechanism (23S rRNA alteration), PoxtA and OptA gene mutations were also reported from the USA and Turkey from resistant Gram-positive clinical isolates [51].

Despite few less susceptible isolates that emerged in some studies with the expression of different genetic mutations, the incidence of TDZ resistance is still low in key clinically relevant bacteria. However, the potential for the emergence of resistance and/or cross-resistance between the two oxazolidinones will remain a concern and warrants active surveillance. Moreover, for isolates with undefined EUCAST susceptibility breakpoints, resistant data are lacking. More systematic investigations are required to define the mutant selection window in relation to the TDZ exposure profile for the entire treatment duration, in order to determine which PK/PD index is related to suppression of resistance development [128].

6 TDZ as a Potential Treatment Option Against *Mycobacterium tuberculosis*

The efficacy against mycobacteria, high pulmonary penetration, and a favorable safety profile compared with LNZ makes TDZ a potential candidate to treat pulmonary tuberculosis caused by *M. tuberculosis* and in non-tuberculosis mycobacteria pulmonary infections [129]. Moreover, its high intracellular activity makes it an ideal potential candidate to treat intracellular mycobacterium tuberculosis infections. The TDZ MIC values against *M. tuberculosis* typically range from 0.125 to 1 mg/L [129–132].

Tedizolid shows superior anti-mycobacterial activity over LNZ and has potential to substitute LNZ in antitubercular combination regimens. When studied in a hollow fiber in vitro infection model against intracellular (disseminated pediatric tuberculosis model) mycobacterium tuberculosis (MIC: 0.5 mg/L) for 28 days ($AUC_{0–24}$ of 0–139.41 mg · h/L, elimination half-life of 12 h), the EC_{80} ($AUC_{0–24}$/MIC ratio associated with 80% maximum bacterial kill) of TDZ

associated with an optimal log kill and time to positivity (TTP) was nearly identical (184 vs 189) [133]. In a comparative study with a comparable EC_{80} (TDZ 238.4 [MIC: 0.5 mg/L] vs LNZ 24.05 [MIC: 1 mg/L]), TDZ showed a >10,000-fold higher activity than LNZ and hence supports TDZ as the preferable choice in intracellular antitubercular therapy in pulmonary cavities and in disseminated tuberculosis in children [133]. This superior activity of TDZ over LNZ was also observed for *Mycobacterium avium*-intracellular complex in a separate in vitro study [134]. Srivastava et al. further investigated TDZ against semi-dormant mycobacterium tuberculosis (MIC: 0.25 mg/L) in a hollow fiber in vitro infection model, where an EC_{80} of 200 mg · h/L best related to the sterilizing effect (TTP), which was in line with the earlier reported value (188 mg · h/L). Using Monte Carlo simulations, at a human equivalent dose of 200 mg/day ($AUC_{0–24}$ mg/L of 31.0 ± 6.6), >90 % of patients achieved EC_{80} of 200 mg · h/L for an MIC of ≤0.5 mg/L and hence this value was declared as a tentative susceptibility breakpoint [135]. The mitochondrial toxicity, taken as an indirect toxicity predictor, was found lower for TDZ at exposures in the above-mentioned study as compared with LNZ.

The dual combination with TDZ (200 mg/day) and high dose of MXF (800 mg/day) results in sterility (TTP assay) for both log-phase (after 14 days of therapy) and semi-dormant forms (after 42 days of therapy) of mycobacterium tuberculosis in a hollow fiber in vitro infection model [136]. For the non-replicating persisters form, a triple therapy (TDZ 200 mg/day, MXF 800 mg/day, and faropenem twice daily to achieve 66% time above MIC) resulted in sterilization as early as 14 days of therapy compared with 21 days of therapy with the standard regimen (isoniazid 300 mg/day, rifampin 600 mg/day, and pyrazinamide 1.5 g/day) [136].

The above-mentioned results favor TDZ as an alternative to replace LNZ in MDR/XDR-TB therapeutic regimens while a dose of 200 mg/day can be a potential dose taken forward to these clinical studies. Combination therapy in mycobacterium tuberculosis is usually favored for clinical success, better patient compliance, safety, and prevention of drug resistance, and hence the combination regimen, in particularly the triple therapy of TDZ, MXF, and faropenem, might be a favorable antibiotic combination to be further investigated in human studies. Although the in vitro results for a short duration (42 days) propose comparable safety of TDZ, the long-term safety profile of TDZ therapy in patients with tuberculosis is lacking.

7 Conclusions

Tedizolid demonstrates broad in vitro and in vivo efficacy against a number of clinically important Gram-positive pathogens including MRSA and VRE. It is a viable treatment option against skin and skin-structure infections caused by these bacteria. Tedizolid has several advantages over LNZ with regard to dosing frequency and its safety profile. Further research is required to investigate the contribution of the immune system to the efficacy of TDZ. Results from murine pulmonary models, PK studies in healthy volunteers, and a recent comparative clinical trial indicate its potential use in pulmonary infections, but more data on safety in long-term use are needed to establish its role in mycobacterium tuberculosis treatment. Research in further potential clinical applications is warranted.

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