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Comparison of the in vitro activity of tedizolid, linezolid, and vancomycin against Staphylococcus aureus isolates collected in China (2013–2014)

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ABSTRACT

Objectives

Tedizolid phosphate is a novel oxazolidinone antibiotic under clinical development in China against infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). TZD is typically at least 4-fold more potent (MIC_{90}: 0.5 µg/mL) *in vitro* than linezolid (MIC_{90}: 2.0 µg/mL) against Gram-positive pathogens, including strains resistant to linezolid or vancomycin. TZD has recently been approved in the US for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSIs). A Phase 3 study in patients with ABSSSI is ongoing in China. The current surveillance study presented here was undertaken to analyse the activity of TZD in comparison with linezolid and vancomycin against *S. aureus* in order to monitor trends in antibacterial susceptibility in China.

Methods

A total of 663 *S. aureus* isolates were collected from 10 sites across China between 2013 and 2014. Isolates were obtained from Chinese patients with skin and soft tissue, respiratory tract, bloodstream, or other sites of infections. Broth microdilution testing using frozen panels according to CLSI guidelines was performed at IHMA and Eurofins laboratories in the US. *In vitro* activity of TZD, linezolid, and vancomycin was tested by evaluating minimum inhibitory concentration values (MICs).

Results

Of the 663 *S. aureus* isolates collected, 425 were MRSA and 238 were methicillin-susceptible *S. aureus* (MSSA). TZD demonstrated high *in vitro* activity against *S. aureus* with equal potency against both MRSA and MSSA, producing MICs ranging from 0.12 to 0.5 µg/mL and MIC_{90} values of 0.5 µg/mL (Table 1). Against both MSSA and MRSA, TZD was 2-fold more potent than vancomycin and 4-fold more potent than linezolid based on MIC_{90} values (Table 1). Using FDA breakpoints, all *S. aureus* isolates were susceptible to tedizolid.

Conclusion

TZD was highly potent against *S. aureus* in China, showing equal potency against both MRSA and MSSA, and was 2- to 4-fold more potent than vancomycin or linezolid. The results were consistent with those of previous reports among isolates from other regions including the US, Europe, Latin America, and Pacific Rim.

Table 1. *In vitro* activity of TZD, LZD, and VAN against *S. aureus*, MRSA, and MSSA

	TZD			LZD			VAN		
	MIC_{90} (µg/mL)	Range (µg/mL)	S (%)	MIC_{90} (µg/mL)	Range (µg/mL)	S (%)	MIC_{90} (µg/mL)	Range (µg/mL)	S (%)
S. aureus (All) (N=663)	0.5	0.12-0.5	100	2	0.5-4	100	1	≤0.25-2	100
MRSA (N=425)	0.5	0.12-0.5	100	2	0.5-4	100	1	≤0.25-2	100
MSSA (N=238)	0.5	0.12-0.5	100	2	0.5-4	100	1	≤0.25-2	100

S: susceptible; LZD: linezolid; TZD: tedizolid; VAN: vancomycin

INTRODUCTION

- Gram-positive infections caused by drug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) remain a challenge for physicians as patients often have poorer outcome when compared with methicillin-susceptible *S. aureus*.[1]
- *S. aureus* is the predominant cause of acute bacterial skin and skin structure infections (ABSSSIs) and frequently of nosocomial pneumonia.[1,2] The prevalence of MRSA ranges from 20 to 70% worldwide.[3]
- Tedizolid (TZD) 200 mg, once daily, intravenous (IV) and/or oral (PO), treatment for 6 days has recently been approved for the management of patients with ABSSSIs caused by key Gram-positive pathogens in the US, Canada and Europe.[4] TZD 200 mg, once-daily for 6 days has demonstrated non-inferior efficacy with shorter treatment duration to linezolid (LZD) 600 mg, twice daily for 10 days in patients with ABSSSIs in two pivotal double-blind Phase 3 randomised clinical trials.[5,6]
- TZD demonstrated an improved safety profile compared with linezolid, with significantly lower proportions of patients experiencing gastrointestinal adverse events or platelet counts below the lower limit of normal.[5,6]
- TZD has high *in vitro* potency against Gram-positive pathogens, including clinical isolates of methicillin-susceptible SA (MSSA) and MRSA.[7] The potency of TZD is at least 4-fold greater than that of LZD against *S. aureus*, enterococci or streptococci.[7,8,9]
- Monitoring the susceptibility of clinical pathogens globally is necessary to understand potential resistance development. The objective of this study was to compare susceptibility of SA, MSSA and MRSA to TZD, LZD and vancomycin (VAN), using isolates from China collected in 2013–2014.

METHODS

- Non-duplicate, non-consecutive single-patient clinical isolates obtained from 10 institutions across China in 2013 and 2014 were submitted and tested centrally. There were two central laboratories: 1) IHMA Inc. located in Schaumburg, Illinois, USA and 2) Eurofins Medinet Inc. located in Chantilly, Virginia, USA. Susceptibility testing was done using broth microdilution according to CLSI M07 and M100 guidelines.[10,11]
- Susceptibility breakpoints (MIC, µg/mL) for TZD approved by the FDA are: Susceptible: ≤0.5 µg/mL; Intermediate: 1 µg/mL; Resistant: ≥2 µg/mL.[12]
- The isolates were collected from patients with skin and soft tissue infections, respiratory tract infections, bacteraemia, and from miscellaneous other infections.
- Although susceptibility to 13 antibiotics was tested in this study, only the *in vitro* activity of TZD, LZD, and VAN is presented here.

RESULTS

- A total of 663 *S. aureus* isolates were tested in the study. Of the 663 isolates, 425 (64.1%) were identified as MRSA across Chinese hospitals.
- MIC values for TZD were lower than for LZD or VAN for SA (Figure 1), MSSA (Figure 2) and MRSA (Figure 3). All SA isolates were susceptible to TZD, LZD, and VAN (Figure 1).
- The majority of SA, MSSA, and MRSA isolates had a tedizolid MIC of 0.5 µg/mL (74.2%, 74.8%, and 73.9%, respectively) and linezolid MIC of 2 µg/mL (76.2%, 76.9%, and 75.8%, respectively).
- No isolate was found with a tedizolid MIC of 1 µg/mL (intermediate susceptibility) or ≥2 µg/mL (resistant) (Figure 4).
- All *S. aureus* isolates were within the susceptible range for TZD (Susceptible: ≤0.5 µg/mL; Intermediate: 1 µg/mL; Resistant: ≥2 µg/mL).
- The scatterplot (Figure 4) shows that all the *S. aureus* strains were within the susceptible range for LZD, and only 12 isolates had MIC 4 µg/mL (Susceptible: ≤4 µg/mL; Resistant: ≥8 µg/mL).
- Among the 663 isolates tested, the two most prominent phenotypes were isolates that had TZD and LZD MICs of 0.5 µg/mL and 2 µg/mL, respectively (472/663 [71.2%]); and TZD and LZD MICs of 0.25 µg/mL and 1 µg/mL, respectively (124/663 [18.7%]). (Figure 4).

CONCLUSIONS

- TZD exhibited the most potent *in vitro* activity among the agents presented here against both MRSA and MSSA in China isolated in 2013–2014.
- There was a good correlation in the susceptibility of all *S. aureus* isolates between tedizolid and linezolid based on the respective MIC values, supporting the use of susceptibility to linezolid as a surrogate marker of susceptibility to tedizolid.[12]
- The results of TZD *in vitro* potency in China were consistent with those of previous reports among isolates from other regions including the US, Europe, Latin America, and Pacific Rim.[13]
- The results support the continued global clinical development of TZD for ABSSSI in China and nosocomial pneumonia globally.

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Figure 1. Tedizolid (TZD), linezolid (LZD) and vancomycin (VAN) MIC Distributions against all *Staphylococcus aureus* (N=663) isolates from China.

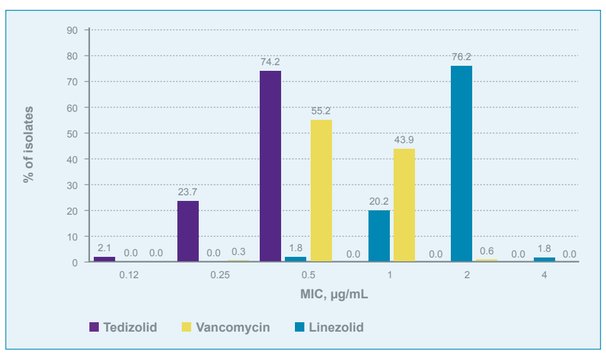

Figure 2. Tedizolid (TZD), linezolid (LZD) and vancomycin (VAN) MIC Distributions against MSSA (N=238) isolates from China.

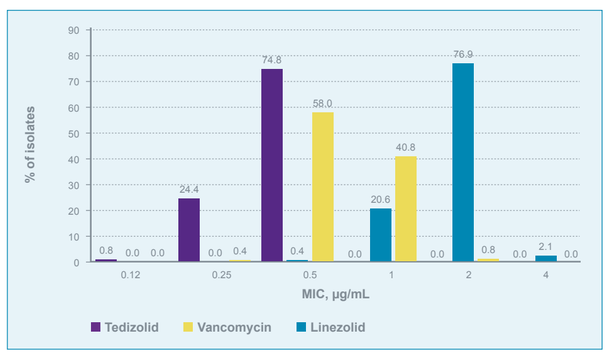

Figure 3. Tedizolid (TZD), linezolid (LZD) and vancomycin (VAN) MIC Distributions against MRSA (N=425) isolates from China.

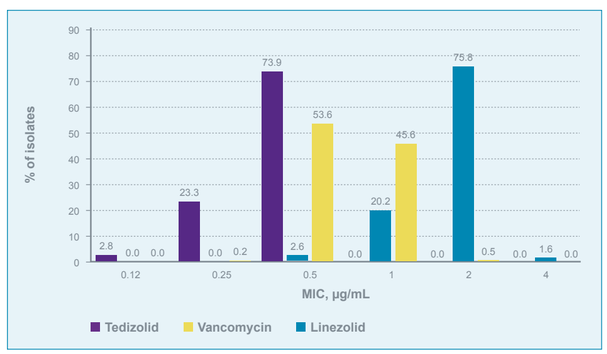

Figure 4. Tedizolid (TZD) vs Linezolid (LZD) MIC Values Scatterplot for *S. aureus* isolated in 2013–2014 in China (N=663).