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An *in vitro* evaluation of the efficacy of tedizolid: implications for the treatment of skin and soft tissue infections

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Abstract

Skin and soft tissue infections (SSTI) are among the most commonly occurring infections and evidence suggests that these are increasing world-wide. The aetiology is diverse, but *Staphylococcus aureus* predominate and these are often resistant to antimicrobials that were previously effective. Tedizolid is a new oxazolidinone-class antibacterial indicated for the treatment of adults with SSTI caused by Gram-positive pathogens, including *S. aureus*.

The aim of this study was to evaluate the *in vitro* efficacy of tedizolid in comparison to other clinically used antibacterials against antibiotic sensitive- and resistant-staphylococci, grown in planktonic cultures and as biofilms reflecting the growth of the microorganism during episodes of SSTI.

Against a panel of 66 clinical staphylococci, sensitivity testing revealed that a lower concentration of tedizolid was required to inhibit the growth of staphylococci compared to linezolid, vancomycin and daptomycin; with the tedizolid MIC\textsubscript{50} being 8-fold (*S. aureus*) or 4-fold (*S. epidermidis*) below that obtained for linezolid. In addition, *cfr*\textsuperscript{+} linezolid-resistant strains remained fully susceptible to tedizolid. Against *S. aureus* biofilms, 10×MIC tedizolid was superior or comparable with 10×MIC comparator agents in activity, and superior to 10×MIC linezolid against those formed by *S. epidermidis* (65 vs. 33% reduction, respectively). Under flow-conditions both oxazolidinones at 10×MIC statistically out-performed vancomycin in their ability to reduce the viable cell count within a *S. aureus* biofilm with fewer the 12% of cells surviving compared to 63% of cells.
In conclusion, tedizolid offers a realistic lower-dose alternative agent to treat staphylococcal SSTI, including infections caused by multi-drug resistant strains.

Keywords: skin and soft tissue infections, tedizolid, linezolid, staphylococcus, biofilm, minimum inhibitory concentration

Abbreviations:

CFU, colony forming unit
DAP, daptomycin
DMSO, dimethyl sulfoxide
EUCAST, European Committee on Antimicrobial Susceptibility Testing
GMO, genetically modified organism
LZD, linezolid
MRSA, methicillin resistant Staphylococcus aureus
MSSA, methicillin sensitive Staphylococcus aureus
MIC, minimum inhibitory concentration
MHB, Mueller-Hinton broth
PBS, phosphate buffered saline
SSTI, skin and soft tissue infection
TZD, tedizolid
VAN, vancomycin
VISA, vancomycin intermediate susceptibility S. aureus
1. Introduction

Skin and soft tissue infections (SSTIs) are common within both hospitalised patients and individuals within the community, yet providing a suitable treatment remains a clinical challenge. Published national and international guidelines for the treatment of SSTIs broadly agree [1]. The United Kingdom’s National Institute for Clinical Excellence (NICE) guidelines, for example, emphasise the importance of using empirical treatment effective against methicillin resistant *Staphylococcus aureus* (MRSA) [1]. With the subsequent knowledge of bacterial cultures, treatment can be de-escalated to a narrow spectrum agent, preferably with oral administration allowing treatment to continue in the community. In reality, a microbiological diagnosis may not be available and initial therapy inadequate leading to clinical failure, recurrence of infection and readmission to hospital increasing the overall length of patient stay. Complicating therapy further, resistant *Staphylococcus aureus* can be responsible for in the region of half of complicated SSTIs, yet empirical therapy is often not appropriate for these microorganisms [2].

Currently vancomycin, linezolid, daptomycin, ceftaroline and telavancin are among those antibacterials recommended for the treatment of severe SSTIs with other agents in reserve for milder infections [3]. Newer agents are becoming available, including tedizolid, dalbavancin and oritavancin, but clinical evidence for the role of these agents is limited and needs to be provided if future guidelines are to be established [4].

Tedizolid phosphate (Sivextro®) is a next-generation oxazolidinone antibacterial approved for the treatment of adults with acute SSTIs caused by susceptible Gram–positive microorganisms, including staphylococci [5]. The spectrum of activity is similar to linezolid,
though activity is retained against some strains that are resistant to linezolid [6]. Similar in
mode of action to other oxazolidinones, antibacterial activity is mediated by inhibiting
protein synthesis [7].
Tedizolid is a new drug approved for the treatment of SSTIs in a number of countries,
including the United States, Canada and the European Union [4]. The aim of this study was
to evaluate the *in vitro* efficacy of tedizolid in comparison to other clinically used
antibacterials against antibiotic sensitive and resistant staphylococci, grown in planktonic
cultures and as biofilms reflecting the growth of the microorganism during episodes of SSTI.
2. Material and Methods

2.1. Strains, culture conditions and preparation of antibiotics

The study included 66 clinical staphylococcal isolates: 27 methicillin sensitive \textit{S. aureus} (MSSA) (including two linezolid-resistant), 27 MRSA (including two linezolid-resistant) and 12 \textit{Staphylococcus epidermidis} (including two linezolid-resistant). Except the six linezolid-resistant strains (provided by J. Mingorance, Madrid), all strains were supplied by the Scottish MRSA Reference Laboratory, Glasgow (Supplementary Table 1).

All experiments were performed in Mueller-Hinton broth (MHB, Oxoid); for testing with daptomycin the medium was supplemented with 50 mg/L Ca$^{2+}$ [8].

Tedizolid and linezolid were gifted by MSD and Pfizer, respectively (MSD, Hertfordshire, UK; Pfizer Ltd, Surrey, UK). Vancomycin and daptomycin were purchased from Sigma-Aldrich (Dorset, UK). Stock solutions of tedizolid were prepared in dimethyl sulfoxide (DMSO, 1,600 mg/L) prior to 2-fold dilutions in DMSO as per the supplier’s guidelines. Other antibiotic stocks of 10,000 mg/L (except linezolid 1,000 mg/L) were prepared using distilled water and used or stored at -20°C for a maximum of two weeks.

2.2. Antibiotic susceptibility of staphylococcal planktonic cultures

The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were evaluated for vancomycin, daptomycin and linezolid according to EUCAST guidelines [8]. For tedizolid, using 96-well plates, 2 µL of the relevant 50× tedizolid was combined with 98 µL of an overnight culture adjusted to 5×10^5 cfu/mL. \textit{S. aureus} ATCC
29213 was included as a control strain; all results were within guideline limits. MIC/MBCs were repeated independently at least three times.

2.3 Time-kill assays

The time-kill kinetics were determined for two MRSA isolates; one linezolid-sensitive and one linezolid-resistant. Overnight cultures were diluted to a final concentration of $1 \times 10^6$ cfu/mL in 50 mL fresh MHB (antibiotic-free control) and MHB supplemented with each antibiotic (tedizolid, linezolid and vancomycin) at a concentration of $0.25 \times$, $1 \times$ and $10 \times$MIC and then incubated at $37^\circ$C with aeration at 200rpm for 24 h. Aliquots of 1 mL were removed at time zero and then every 30 minutes for the first 6 h and finally 24 h post-inoculation and viable counts obtained. Experiments were performed in triplicate.

2.4. Antibiotic susceptibility of biofilms

Twenty robust biofilm forming strains, selected using the crystal violet staining technique (data not shown), were evaluated for antibacterial susceptibility whilst in a biofilm mode of growth; 5 each MRSA, MSSA, *S. epidermidis* and linezolid-resistant *Staphylococcus* strains. Overnight cultures adjusted to $1 \times 10^6$ cfu/mL were inoculated into 96-well plates and incubated for 24 h at $37^\circ$C on a rocking platform (60 oscillations/min). Then, supernatants were removed, biofilms washed three times with phosphate buffered saline (PBS, Oxoid) and 150 µL of antibiotic supplemented MHB added at concentrations of $0.25 \times$, $1 \times$, $10 \times$ or $100 \times$MIC (except where $100 \times$MIC exceeded $C_{\text{max}}$). Antibiotic-free controls were included. After 24 h antibiotic exposure at $37^\circ$C, 0.001% (v/v) resazurin (Sigma) in PBS was added to each washed biofilm and incubated at $37^\circ$C in the dark for 2 h, then fluorescence measured (EM$_{590\text{nm}}$/EX$_{540\text{nm}}$) using a plate reader (FLUOstar Optima, BMG Labtech, Germany),
providing an indirect measure of the viable cells. The experiment was repeated on two further occasions. Any significant outliers among technical replicates were determined using Grubbs’ test (p-value <0.05) and excluded from further analysis. Using the fluorescence readings, the percentage of cells surviving within an antibiotic-treated biofilm was determined by comparison with the untreated control. Statistical difference between treated and untreated biofilms was determined using Student’s t-test and GraphPad Prism 7 Software.

2.5. Tedizolid susceptibility of biofilms under flow-conditions

A flow-cell system was used to evaluate susceptibility under conditions replicating the in vivo environment. Three silicone coupons were placed in each of two chambers of a FC 275 flow-cell (BioSurface Technologies Corporation, Montana, USA) and MHB introduced into the system via two reservoirs. Using overnight cultures of MSSA31, the coupons were inoculated with 1×10^6 cfu/mL and maintained under static conditions for 1 h at 37°C to aid attachment, and then media flow (1 mL/minute) continued for 3 days during biofilm formation. Subsequently, one reservoir was replaced with fresh MHB (antibiotic-free control) and the second with MHB supplemented with 10×MIC tedizolid, linezolid or vancomycin and flow resumed for a further 24 h at 37°C. Finally, the coupons were removed, rinsed and individually sonicated 3×5 minutes in PBS using a sonicating waterbath and viable counts determined. Each experiment was performed either in duplicate or triplicate. Percentage cell survival was calculated (section 2.4) and statistical difference between treated and untreated biofilms determined using Student’s t-test.
3. Results

3.1. Antibiotic susceptibility of planktonic cultures

The MICs and MBCs were determined against the 66 staphylococci (Supplemental Data Table 1). There was no evidence of resistance to any of the antibiotics tested, except for the Spanish strains that were resistant to linezolid, and all the MIC ranges and MIC₅₀ values for linezolid, vancomycin and daptomycin were as expected being within one-dilution of the EUCAST published data [8] (Supplemental Data Table 1). All the linezolid-sensitive strains were highly susceptible to tedizolid with MICs within the narrow range of 0.125-0.5 mg/L; a median MIC value 8-fold below that of linezolid. The tedizolid sensitivity of linezolid-resistant strains varied with the resistance mechanism; those cfr⁺ had a tedizolid MIC of 0.25-0.5 mg/L (versus 8 mg/L linezolid), those that possessed the G2576T mutation had tedizolid MIC values of 2-4 mg/L (versus 16-64 mg/L linezolid), whilst the strain exhibiting both linezolid-resistance mechanisms had MIC values of 4 mg/L tedizolid and 512 mg/L linezolid.

Vancomycin and daptomycin were shown to be bactericidal, with only 16% and <1% of isolates presenting with a MBC:MIC ratio ≥8. By contrast linezolid and tedizolid were bacteriostatic (Supplemental Data Table 1).

3.2 Time-kill kinetics

Time-kill kinetics were determined for tedizolid, linezolid and vancomycin for two MRSA strains; one sensitive (MRSA23) and one resistant (cfr⁺ JM02) to linezolid (Fig.1). Sub-MIC antibiotic exerted minimal effect on the growth of the organisms with viable bacterial cell concentrations remaining similar to the untreated control. At 1× and 10×MIC tedizolid was
bacteriostatic against both isolates with activity against the linezolid-resistant strain comparable to that exerted against the sensitive strain (Fig.1). Despite initially impeding growth, 1×MIC linezolid failed to inhibit growth of \textit{cfr}^+ \textit{JM02} with a 2-log increase in bacterial cell number compared to the initial inoculum after 24 h exposure to the agent (10×MIC exceeded the therapeutically achievable concentration and was not tested). Conversely, a >3-log reduction in viable cell number in comparison to the initial inoculum was attained after 24 h exposure to 1× and 10×MIC vancomycin confirming the bactericidal nature of the agent.

3.3. Antibiotic susceptibility of biofilms

A dose-dependent response was noted for biofilms challenged with each antibacterial. At a concentration of 1×MIC, no agent was able to reduce the proportion of viable cells within the biofilm to 60% or fewer of untreated control biofilm; vancomycin in particular had little if any impact (Fig.2a). The mean level of activity exerted against \textit{S. epidermidis} isolates (77-107% mean survival) by each antibacterial was inferior to that exhibited against the \textit{S. aureus} isolates (64-103% mean survival), an effect that was of particular note with linezolid (103% vs 64% mean survival, \textit{S. epidermidis} and \textit{S. aureus} respectively).

When challenged with 10×MIC antibacterial there was a marked reduction in the proportion of cells within the biofilm remaining viable (28-77% mean cells remaining viable) (Fig.2b). Against \textit{S. aureus} all of the agents tested reduced the biofilm to below a 50% mean of the untreated control (28-45% mean cell survival) compared to \textit{S. epidermidis} where only vancomycin and tedizolid attained a comparable reduction (29 and 35% mean cell survival, respectively); linezolid and daptomycin achieved only a 33% and 47% mean decrease in
viable cells, respectively, with the majority of cells remaining viable after treatment. In addition to the greater level of tolerance exhibited by *S. epidermidis* isolates, there was also greater variation in susceptibility between the strains. At least one *S. epidermidis* isolate was unaffected by 10×MIC of any agent tested (97-103% cell viability), the exception being tedizolid which retained a good level of activity against all the *S. epidermidis* strains tested, including the linezolid-resistant strains.

Under flow-conditions tedizolid was superior to vancomycin and comparable to linezolid in the ability to reduce the proportion of viable biofilm-associated cells remaining on the silicone coupons (Fig.3). Exposure to 10xMIC tedizolid or linezolid led to a statistically significant reduction in the proportion of viable cells remaining within the biofilm (8%, p <0.05 or 12%, p <0.005 cell survival compared to the untreated control, respectively) while vancomycin did not achieve a statistically significant reduction in viable cells (63%, p=0.08).
4. Discussion and Conclusion

Ranging from mild to life-threatening, SSTI are among the most commonly occurring infections and evidence suggests that these are increasing. From 1993-2005, the number of emergency department visits in the USA by patients with these presentations increased from 1.2 million visits to 3.4 million [9]. Whilst SSTIs are diverse in aetiology, *S. aureus* are consistently predominating world-wide with multi-drug resistant strains increasingly being reported [10]. In the USA, one study reported that 81% of culture-positive SSTIs were caused by *S. aureus*, with almost half (46%) of those strains recovered being resistant to methicillin [11]. The high prevalence of the USA300 MRSA strain may account in part for these figures. In Europe however, where USA300 remains typically rare, a similar profile is seen. Morrissey *et al.* (2012) reported that approximately one half of SSTIs caused by *S. aureus* were MRSA [12]. As such, SSTIs pose an immense, and increasing, physical and economic burden to healthcare providers.

Achieving an effective treatment combining surgical debridement or drainage with empirical antibiotic therapy is not without its challenges. From the microbiological prospective, the agent is often unknown, multidrug-resistance is prevalent and a biofilm mode of growth complicates therapy. Though more prevalent in chronic wounds with 60% of samples being positive, biofilms have also been detected in 6% of acute wounds [13]. In this study, the increased activity of tedizolid compared to linezolid and other anti-staphylococcal agents was achieved typically using lower concentrations against both planktonic and biofilm-associated cells, including *cfr*+ multidrug-resistant strains. Against *S. aureus* biofilms, tedizolid was superior or comparable with comparator agents in activity, and typically superior against those formed by *S. epidermidis* strains. Under flow-conditions mimicking
the *in vivo* environment of a SSTI, for example infection related to an indwelling-device, the bacteriostatic oxazolidinones both out-performed vancomycin.

Vancomycin has been a mainstay of treatment for staphylococcal SSTI. However, the decreased susceptibility observed in vancomycin intermediate susceptibility *S. aureus* (VISA) and strains displaying heteroresistance, the need for intravenous slow-infusion and to monitor serum levels, and the potential for toxicity have led to moves towards other antibacterial agents. The alternatives currently available include linezolid, telavancin and daptomycin. Linezolid has been shown to be more effective at treating SSTIs than vancomycin with fewer complications being reported and patient discharge occurring sooner [14]. Whilst linezolid retains a good level of activity against staphylococci [15], the emergence of linezolid resistance in staphylococci is a concern [16]. Tedizolid has however, been demonstrated by this study to retain activity against *cfr*+ staphylococci. It has previously been reported that the sterically compact nature of the hydroxymethyl group of tedizolid greatly improves activity against strains possessing the *cfr* gene [6]. In addition, tedizolid was reported by Russo *et al.* (2016) to be statistically non-inferior to linezolid in patients with SSTI for an early clinical response evaluated 48–72 h after beginning therapy [17]. Other factors favouring the use of tedizolid over contemporary agents in the treatment of SSTI include the long half-life (double linezolid) allowing once a day dosing, short course duration and an easy switch from intravenous to oral administration. It is recognised that these studies are undertaken *in vitro* and as such cannot infer *in vivo* activity, however, the data generated suggest that tedizolid offers an additional drug choice for the treatment of SSTIs.
In conclusion, in this *in vitro* study the anti-staphylococcal activity of tedizolid has been shown to be at least comparable and often superior to comparator agents that are routinely prescribed in the treatment of SSTIs. Taken with the drive to de-escalate SSTI treatment sooner, switching early to a short-course oral agent allowing early discharge, tedizolid offers a realistic lower dose alternative agent in the treatment of staphylococcal SSTI, including those where biofilms are present.

Acknowledgements

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Some of the data presented in this manuscript has previously been reported at the 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Vienna 22-25 April 2017 and the Microbiology Society Annual Conference 2017, Glasgow 3 – 6 April 2017.

Declarations

Funding: This work was supported MSD/Merck (MISP#53795). The funders had no role in study design, data collection or analysis.

Competing Interests: None
Ethical Approval: Work involving the transconjugate strain *Staphylococcus aureus* ATCC 29213 *cfr* was performed under The Genetically Modified Organisms (Contained Use) Regulation 2014 of the Health and Safety Executive.
References


[14] Yue JD, BR; Yang, M; Chen, X; Wu, T; Liu, G. Linezolid versus vancomycin for skin and soft tissue infections. Cochrane Library. 2016.


**Figure Legends**

**Figure 1.** Time-kill kinetics of linezolid sensitive MRSA23 (a,c,e) and linezolid resistant MRSA (cfr+) JM02 (b,d,f) challenged with (a,b) tedizolid, (c,d) linezolid and (e,f) vancomycin at concentrations of 0.25xMIC (♦), 1xMIC (▲), 10xMIC (■), compared to untreated control cultures (•). Error bars represent SEM between replicate samples (n = 3). Broken line (-----) indicates a 3-log reduction in viable cell number in comparison to the initial inoculum. cfu, colony forming units.

**Figure 2.** Susceptibility of biofilm-associated staphylococcal cells exposed to (a) 1×MIC or (b) 10×MIC antibiotic compared to untreated control cultures. Antibiotics included VAN, vancomycin; DAP, daptomycin; LZD, linezolid; TZD, tedizolid. Cell survival was assessed using the metabolic dye resazurin. Each experiment consisted of four replicate biofilms and was repeated a further two times. Error bars represent SEM.

**Figure 3.** Susceptibility of MSSA31 biofilm-associated cells cultivated on silicone rubber coupons and exposed to 10xMIC antibiotic under flow conditions within a BST flow-cell system. Antibiotics included VAN, vancomycin; LZD, linezolid; and TZD, tedizolid. Paired t-test; ** p-value < 0.05; **** p-value < 0.005; no asterisk p > 0.05. Each experiment consisted of three replicate silicone rubber coupons and a minimum of two independent repeats.
**Supplementary Table 1.** Origin of the strains used in this study.

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<th>Sample type</th>
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<th>Isolated</th>
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<td>2011-13</td>
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*a; Hospital Universitario La Paz, Madrid or Scottish MRSA Reference Laboratory (SMRSARL), Glasgow Royal Infirmary, Glasgow.

b; Isolates represented 32 different spa types (1-9 representatives per spa type with t032 being predominant) and 12 clonal complexes (with CC22, n = 20; CC5, n = 6; and CC30, n = 5 being the principal types).

nk; not known.
Supplemental Table 2. Antibiotic susceptibility of staphylococci grown in planktonic culture.

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<td>MRSA</td>
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<td>4</td>
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MSSA, n = 27 including 2 linezolid resistant strains; MRSA, n = 27 including 2 linezolid resistant strains; S. epidermidis, n = 12 including 2 linezolid resistant strains.