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In vitro activity of Tedizolid and Dalbavancin against MRSA strains is dependent on infection source

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ABSTRACT

Objective: We tested the *in vitro* susceptibility to Tedizolid and Dalbavancin of Methicillin-resistant *Staphylococcus aureus* strains recovered from blood and wound cultures, and compared our results with studies conducted in the last four years. We examined whether the *spa* types affect the susceptibility of the different strains.

Methods: We analyzed 275 Methicillin-resistant *S. aureus* strains recovered from 128 blood and 147 wound samples. For each strain, we performed minimum inhibitory concentration for Tedizolid and Dalbavancin and *spa* typing. We also performed a non-systematic review of the worldwide literature from the last four years concerning the *in vitro* activity of Tedizolid and Dalbavancin using the PubMed database; results were restricted by date of publication, between January 2015 and January 2018.

Results: We found one Dalbavancin-resistant isolate (0.36%) and no resistance to Tedizolid. The minimum inhibitory concentration values were dependent in the strain source (wound vs. blood) for both antibiotics. For Dalbavancin, there was also dependence on the *spa* type.

Conclusion: This study indicates Tedizolid and Dalbavancin have potent *in vitro* activity against the prevalent *S. aureus* clones in Israel. Further studies should be performed in order to uncover the factors contributing to reduced susceptibility of *S. aureus* strains to new drugs.

Introduction

Staphylococcus aureus is one of the most common causes for human diseases. This Gram-positive bacterium causes various infections, ranging from skin and soft tissue infections, to pneumonia, meningitis, and sepsis (Tatarkiewicz et al., 2016). *S. aureus* infections are frequent in both community and health-care institutes, and result in high morbidity and mortality rates and high costs (Purrello et al., 2016).

The emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) and the *S. aureus* ability to gain various resistance mechanisms (Múnera et al., 2017) are a serious health problem worldwide. In addition to the resistance to beta-lactam antibiotics, MRSA strains have developed various forms of resistance to other antimicrobial agents, including for example reduced susceptibility to daptomycin and inducible resistance to macrolides (Purrello et al., 2016). Consequently, the variety of alternatives for treatment of severe MRSA infections is very limited (Múnera et al., 2017).

The prevalence of MRSA has decreased in recent years, probably due to infection control efforts (Karlowsky et al., 2017). However, MRSA infections still lead to high mortality rates (Stryewski and Corey, 2014). Thus, development of new antibiotics is required.

Serious MRSA infections are mostly treated with Vancomycin (Múnera et al., 2017; Purrello et al., 2016; Stryewski and Corey, 2014). However, the frequent use of Vancomycin has resulted in increased minimum inhibitory concentration (MIC), development of reduced or intermediate susceptibility strains, and increased mortality rates (Múnera et al., 2017; Purrello et al., 2016).

In 2014, the U.S. Food and Drug administration (USFDA) approved new antimicrobial agents, Dalbavancin and Tedizolid, for treatment of acute bacterial skin and skin-structure infections caused by MRSA (Tatarkiewicz et al., 2016).

Dalbavancin is a lipoglycopeptide that inhibits cell-wall synthesis, as is Vancomycin. It is benefited with a long half-life that enables a more convenient dosing regimen. Tedizolid, belonging to the oxazolidinone antimicrobial family, suppresses protein synthesis via binding to the 50S ribosomal subunit. It is

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more potent than Linezolid, a previously approved oxazolidinone (Karlowsky et al., 2017).

The current study aimed to compare the *in vitro* susceptibility to two of the new drugs, Tedizolid and Dalbavancin, between MRSA strains recovered from blood and wound cultures. These antibiotics have not yet been used in Israel; therefore, we wanted to evaluate the bacteria's susceptibility to these new antibiotics prior to their use. We conducted a non-systematic review of the literature in order to compare our results with previously studies published in the four recent years. Additionally, we wanted to test whether *spa* types and Panton–Valentine leukocidin (*pvl)* toxin presence affect the susceptibility of the different strains. *Spa* typing of *S. aureus* isolates is an important tool for clonal analysis that can indicate on the virulence of specific *S. aureus* strains (Kolawole et al., 2013). The Panton–Valentine leukocidin (PVL) exotoxin encoding gene, one of the bacteria's virulence factors, is mostly associated with community-acquired MRSA (Velasco et al., 2015).

Materials and methods

Sample collection

The study was performed at the Clinical Microbiology Laboratory of the Baruch Padeh Medical Center, Poriya, in northern Israel and at the *Staphylococcus aureus* National Reference Center of the Israel Ministry of Health, Jerusalem. The study included 275 MRSA strains that were isolated from blood and wound samples of patients (age range: 0–100 years) admitted to various medical institutes in Israel between May 2015 and February 2017 and sent to the *Staphylococcus aureus* National Reference Center of the Israel Ministry of Health. These strains, recovered from 128 blood samples and 147 wound samples, were Panton–Valentine leucocidin (*pvl*)-negative (hospital-acquired strains) and *pvl*-positive (community-acquired strains), respectively (Velasco et al., 2015). *S. aureus* ATCC strain 29213 was used as a reference strain.

In vitro *antibiotics susceptibility tests (AST)*

All MRSA strains were grown at 37 ± 1 °C for 18–24 h before conducting susceptibility tests. Following incubation, several colonies were suspended in saline to a turbidity of 0.5 McFarland. The suspension was seeded on a Mueller–Hinton agar plate (Hy Laboratories Ltd., Rehovot, Israel) and then antibiotic test strips (Liofilchem, Italy, NC) were put on each agar plate for Tedizolid and Dalbavancin. Plates were incubated at 35 ± 1 °C for 16–20 h. MIC values were determined after 16–20 h according to EUCAST 2018 guidelines: resistance to Tedizolid is defined at MIC values >0.5 mg/L; resistance to Dalbavancin is defined at MIC values above 0.125 mg/L. MIC results were determined by two laboratory technician on two different days.

spa *typing*

Typing of MRSA strains was performed at the National *Staphylococcus aureus* Reference Center, Central Laboratories, Israel Ministry of Health, as previously described (Kahl et al., 2005). Briefly, the *spa* PCR products were sequenced using the BigDye Terminator v1.1 Chemistry (Applied Biosystems, Foster City, CA), according to manufacturer protocol. Cycle sequencing products were purified by gel electrophoresis and analyzed using sequencing Analysis v.5.3.1 software (Applied Biosystems). *spa* typing analysis was performed using BioNumerics 7.5 software.

Literature review

The literature search was performed in May 2018 using the online database PubMed. We used the following search terms: "Tedizolid" or "Dalbavancin" in combination with "MRSA". We restricted results to articles published from January 2015 to May 2018. The reference lists of these articles were also reviewed for additional relevant publications. We included articles of all languages, if an English translation was available. Two authors screened the abstracts of all articles (MA, AP). Review articles were excluded. A total of 20 papers were identified.

Statistical analysis

Chi-square test was applied for analyzing the differences in distribution of MIC values between blood and wound MRSA strains as well as between the different *spa*-types.

The tests were two-tailed and statistical significance was determined with $p < 0.05$.

The statistical analysis was performed using SPSS 17 software (SPSS Inc., Chicago, IL).

Results

The study included 275 MRSA strains that we divided according to their origin into blood and wound strains. One hundred and twenty-eight blood MRSA isolates were *pvl*-negative and one hundred and forty-seven wound isolates were *pvl*-positive.

Figure 1A and B present the distributions of MIC values of MRSA strains for Tedizolid and Dalbavancin, respectively. No resistance to Tedizolid was found. In contrast, one isolate that was recovered from a blood culture was resistant to Dalbavancin, with an MIC value of 0.19 mg/L.

MIC_{50} and MIC_{90} values for tedizolid were 0.25 mg/L and 0.3 mg/L, respectively, in both blood and wound strains (Table 1). For Dalbavancin, MIC_{50} was 0.047 mg/L for both blood and wound strains. MIC $_{90}$ was 0.055 mg/L and 0.06 mg/L for wound and blood isolates, respectively (Table 2).

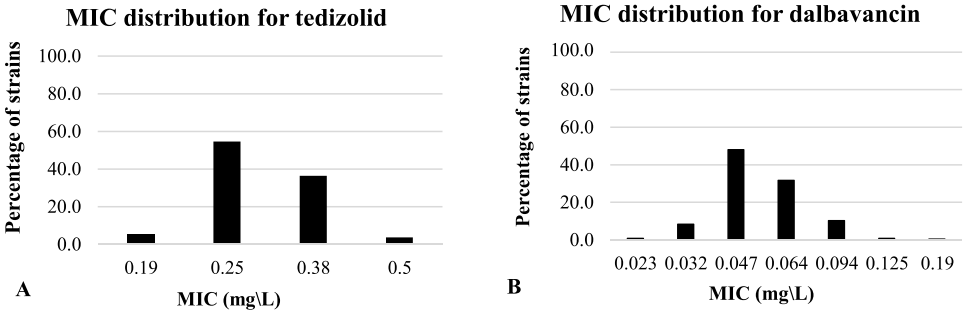

Figure 1. Distribution of MIC values of the different MRSA strains to Dalbavancin (A) and Tedizolid (B).

Table 1
Comparison of MIC distribution of MRSA strains for tedizolid in published papers.

Reference	Year	Country	No. of MRSA strains	Source of MRSA	Tedizolid			
					MIC range	MIC_{50}	MIC_{90}	% Resistance
The current study	**2018**	**Israel**	**275**	**BS, Wounds**	**0.19–0.5**	**0.25**	**0.3**	**0**
Rolston et al. (2018)	2018	USA	20	Not mentioned	0.12–0.25	0.25	0.25	**0**
Múnera et al. (2017)	2017	Colombia	150	SSSI	≤0.19–0.75	0.38	0.5	**0**
Karlowsky et al. (2017)	2017	Asia/Pacific region	1,839	SSSI, BS, Respiratory infections	0.03–0.5	0.25	0.5	**0**
Sweeney et al. (2017)	2017	USA	15	Not mentioned	0.25–0.5	0.25	0.5	**0**
Schmidt-Malan et al. (2017)	2016	USA	35	PJI	0.25–0.5	0.5	0.5	**0**
Barber et al. (2016)	2016	USA	302	Not mentioned	0.03–1	Not determined	0.5	**1.6**
Li et al. (2016)	2016	China	632	HAP, SSSI, BS	0.064–0.5	0.25	0.25	**0**
Peñuelas et al. (2016)	2016	Spain	36	Exudates, BS, Biopsy samples	0.19–0.5 (MRSA) 0.25–1.5 (MLRSA)	0.25 (MRSA)/ 0.75 (MLRSA)	0.4 (MRSA)/ 1 (MLRSA)	**0**
Chen et al. (2015)	2015	Taiwan	100	Pneumonia, SSSI	0.25–0.5	0.25 (SSSI)/ 0.5 (Pneumonia)	0.25 (SSSI)/ 0.5 (Pneumonia)	**0**
Lee et al. (2015)	2015	Seoul, South Korea	90	HAP, SSSI	0.125–0.5	0.5	0.25 (HA-pneumonia)/ 0.5 (SSSI)	**0**

The bold values are the current study's results.
BS = blood samples; SSSI = skin and skin structure infections; PJI = prosthetic joint infection; HAP = hospital-acquired pneumonia; MLRSA = methicillin- and linezolid-resistant *Staph aureus*.

Table 2
Comparison of MIC distribution of MRSA strains for dalbavancin in published papers.

Reference	Year	Country	No. of MRSA strains	Source of MRSA	Dalbavancin			
					MIC range	MIC_{90}	MIC_{50}	% Resistance
The current study	**2018**	**Israel**	**275**	**BS, Wounds**	**0.023–0.19**	**0.055 (wound)/ 0.06 (BS)**	**0.047**	0.36
Guzek et al. (2018)	2018	Poland	124	Wounds, BS, Abscesses, Ulcers, Fistulas.	0.032–0.125	0.125	0.094	**0**
Pfaller et al. (2018)	2018	USA, Europe, Russia, Turkey, Ukraine, Israel.	267	BJI	≤0.03–0.12	0.06	0.06	**0**
Pfaller et al. (2017)	2017	USA	315	SSSI	0.008–0.06	0.06	0.03	**0**
Sweeney et al. (2017)	2017	USA	15	Not mentioned	0.03–0.06	0.06	0.03	**0**
Aktas and Derbentli (2017)	2017	Turkey	30	Not mentioned	0.03–0.12	0.12	0.12	**0**
López Díaz et al. (2017)	2017	Spain	55	Not mentioned	0.06–0.125	0.125	0.125	**Not determined**
Aktas (2016)	2016	Turkey	30	Not mentioned	0.03–0.12	0.12	0.12	**0**
Huband et al. (2016)	2016	Europe, Russia, Turkey, Israel	2,471	Not mentioned	≤0.03–0.25	0.06	0.06	**Breakpoints not available**
Mendes et al. (2016)	2016	USA, Europe, Turkey, Israel, Russia		SSSI	≤0.03–0.5	0.06	0.06	**0.2 (Europe)/0.1 (USA)**
Rolston et al. (2016)	2016	USA	50	Not mentioned	0.008–0.25	0.12	0.03	**Breakpoints not available**
McCurdy et al. (2015)	2015	USA, Europe, Russia, Israel	5,167	Various clinical samples	≤0.03–0.25	0.06	0.06	**0.3**

The bold values are the current study's results.
BS = blood samples; BJI = bone and joint infections; SSSI = skin and skin structure infections.

We investigated whether the source of strain influenced the MIC to each antibiotic agent. We found that there was a dependency of the MIC results in the strain source for both Tedizolid and Dalbavancin ($p < 0.01$) (Table 3). As shown in Table 3, the prevalence of isolates with each MIC value was different between blood MRSA and wound MRSA strains, for both antibiotics. For example, in Tedizolid, while no (0%) wound strain had a MIC value of 0.5 mg/L, 7.8% (10/128) of the blood strains had this MIC value. However, most isolates from both blood and wound origins had an MIC value of either 0.25 mg/L or 0.38 mg/L.

As for Dalbavancin, the differences in distribution of MIC values were observed in every MIC value. For example, 4.1% (6/147) of wound MRSA strains had an MIC value of 0.094 mg/L. In contrast, 17.2% (22/128) of blood MRSA strains had such an MIC value. Additionally, one blood MRSA isolate was resistant to Dalbavancin, while no resistance was observed among wound MRSA isolates. Most strains from blood and wound origins had an MIC value of either 0.047 mg/L or 0.064 mg/L.

We further wanted to test whether the MIC values are affected by the molecular identity of MRSA strains. For this purpose, we

Table 3
Distribution of MIC values of MRSA strains for tedizolid and dalbavancin according to their source.

Antibiotic agent	MIC value (mg\L)	Prevalence (%)		*p* value
		Blood strains (n = 128)	Wound strains (n = 147)	
Tedizolid	**0.19**	7.8	3.4	<**0.01**
	0.25	50	58.5	
	0.38	34.4	38.1	
	0.5	7.8	0	
Dalbavancin	**0.023**	1.6	0	<**0.01**
	0.032	11.7	5.4	
	0.047	43.8	51.7	
	0.064	23.4	38.8	
	0.094	17.2	4.1	
	0.125	1.6	0	
	0.19	0.8	0	

The bold values are the current study's results.

performed *spa* typing of all MRSA strains and compared the MIC results between the different types of strains. As presented in Table 4, no correlation was found between the molecular identity of MRSA strains and their MIC values for Tedizolid ($p > 0.05$). In contrast, we found a dependence of MIC values to Dalbavancin and *spa* type (Table 5). For example, most T001 and T002 strains had high MIC values. In contrast, T437 and T690 showed lower MIC values.

Discussion

Antibiotic resistance is one of the biggest threats to global health. The emergence of clinical MRSA strains with a reduced susceptibility to glycopeptides or a linezolid resistance (Jabés et al., 2004) underscored the need for improvement of existing antimicrobial agents and development of new antibiotics.

This study investigated the *in vitro* antibiotic activity of Tedizolid and Dalbavancin, a new oxazolidinone and a lipoglycopeptide, respectively, against MRSA strains isolated from blood and wounds of patients of all ages.

Similar to previous published data, MRSA strains had no resistance to Tedizolid (Table 1). Only one study, performed in the United States in 2016, reported on 1.6% resistance among 302 MRSA isolates (Barber et al., 2016). In contrast to Israel, where Tedizolid is not yet in use, the United States was the first country that introduced Tedizolid to clinical use, which may explain this resistance rate.

The MIC_{50} and MIC_{90} to tedizolid were relatively low (0.25 mg/L and 0.3 mg/L, respectively), compared to previously reported MIC values in other studies. For example, a study conducted in Columbia in 2017 found MIC_{50} and MIC_{90} of 0.38 mg/L and 0.5 mg/L, respectively, among 150 MRSA isolates recovered from SSSIs (Múnera et al., 2017). MIC_{50} and MIC_{90} of 35 MRSA strains isolated from prosthetic joint infections in the United States were 0.5 mg/L and 0.5 mg/L, respectively (Schmidt-Malan et al., 2017).

As with Tedizolid, our MIC values to Dalbavancin were similar to those found in previous studies (Table 2). Furthermore, the MIC_{50} and MIC_{90} [0.047 mg/L and 0.055 mg/L (wound)/0.06 mg/L (blood), respectively] in the current study are relatively low. For example, MIC_{50} and MIC_{90} of 124 MRSA strains from Poland were 0.094 mg/L and 0.125 mg/L, respectively. The resistance rate to Dalbavancin (0.36%), which is surprising considering the fact that Dalbavancin is not in use in Israel, resembles the resistance rate found in 2015 among MRSA strains collected from the United States, Europe, Russia, and Israel (Schmidt-Malan et al., 2017).

Our main question in the current study was whether the source of infection affects the bacterial susceptibility to Dalbavancin and Tedizolid. We found that the Tedizolid and Dalbavancin MIC values of MRSA strains isolated from wounds tend to be lower compared to isolates from blood. To best of our knowledge, this is the first time that MIC values of different source MRSA strains were found to be statistically different. Most of the studies that had evaluated Tedizolid or Dalbavancin activity did not compare MRSA isolates from different clinical samples. Li et al. (2016) presented the Tedizolid MIC values of MRSA strains from hospital-acquired pneumonia (HAP), blood and SSSI samples, did not find any significant difference between these two groups. However, no statistical test was applied for this question. Similarly, another study presented similar Tedizolid MIC values of MRSA strains from HAP and SSSI samples, without statistical analysis (Lee et al., 2015).

Another conclusion of this study is that MIC values to Tedizolid and Dalbavancin are not dependent on *pvl* presence, meaning that we cannot conclude whether community-acquired MRSA strains are more resistant than hospital-acquired MRSA strains and vice versa.

The *spa* types of the 275 isolates that were tested in this study represent the common *S. aureus* clones isolated from human bacteremia and SSTI cases in Israel. *spa* type had no effect on MIC values to Tedizolid but may have affected MIC values to Dalbavancin; for example, higher MIC values can be seen in *spa* types t001 and t002, but further studies are needed in order to confirm this observation. It is also difficult to compare our results with those of other studies due to differences in the prevalent *spa* types in different areas.

Table 4
Distribution of MIC values of MRSA strains according to their *spa* typing for tedizolid.

spa type	Prevalence of MIC (%)				*p* value
	0.19 (n = 15)	0.25 (n = 150)	0.38 (n = 101)	0.5 (n = 10)	
T001 (n = 33)	20	11.3	10	30	>0.05
T002 (n = 54)	20	18	21	30	
T005 (n = 2)	0	0.7	1	0	
T008 (n = 86)	33.3	34	28	20	
T019 (n = 22)	6.7	8.7	28	20	
T032 (n = 18)	0	8	5	10	
T044 (n = 8)	0	2.7	4	0	
T065 (n = 5)	0	1.3	2.0	10	
T088 (n = 6)	13.3	0.7	3.0	0	
T121 (n = 2)	0	0.7	1	0	
T127 (n = 4)	0	0.7	3	0	
T437 (n = 6)	0	2	3	0	
T596 (n = 2)	0	0	2	0	
T690 (n = 2)	0	1.3	0	0	
T852 (n = 2)	6.7	0	1	0	
Other (n = 23)	0	10	8	0	

Table 5
Distribution of MIC values of MRSA strains for dalbavancin according to their *spa* typing.

spa type	Prevalence of MIC (%)							*p* value
	0.023(n = 2)	0.032 (n = 23)	0.047 (n = 131)	0.064 (n = 87)	0.094 (n = 29)	0.125 (n = 2)	0.19 (n = 1)	
T001 (n = 33)	0	13	4.6	10.3	44.8	100	0	**<0.05**
T002 (n = 54)	100	26.1	17.6	21.8	13.8	0	0	
T005 (n = 2)	0	0	1.5	0	0	0	0	
T008 (n = 86)	0	30.4	39.7	25.3	17.2	0	0	
T019 (n = 22)	0	0	6.1	14.9	3.4	0	0	
T032 (n = 18)	0	17.4	7.6	3.4	0	0	100	
T044 (n = 8)	0	0	0.8	0	0	0	0	
T065 (n = 5)	0	4.3	3.1	0	0	0	0	
T088 (n = 6)	0	0	2.3	0	10.3	0	0	
T121 (n = 2)	0	0	0	2.3	0	0	0	
T127 (n = 4)	0	0	0.8	1.1	6.9	0	0	
T437 (n = 6)	0	4.3	2.3	2.3	0	0	0	
T596 (n = 2)	0	0	1.5	0	0	0	0	
T690 (n = 2)	0	4.3	0.8	0	0	0	0	
T852 (n = 2)	0	0	1.5	0	0	0	0	
Other (n = 23)	0	0	9.2	10.3	3.4	0	0	

The bold values are the current study's results.

Overall, both antibiotics showed potent *in vitro* activity against MRSA strains from different infection types and different patients (with different morbidity and age), as was shown in previous studies (Múnera et al., 2017; Lee et al., 2015; Li et al., 2016). Moreover, both antibiotics were effective against different spa types and *pvl* presence did not affect susceptibility. Thus, these results indicate that both antibiotics are promising and useful for treatment of infections other than the approved indication – SSSIs.

To conclude, this study indicates Tedizolid and Dalbavancin potency against the prevalent *S. aureus* clones in Israel. Further studies should be performed in order to uncover the factors contributing to reduced susceptibility of MRSA strains to new drugs.

Ethical committee

This study was approved by The Baruch Padeh Medical Center, Poriya Ethics Committee.

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Conflict of interest

The authors declare that they have no competing interests.

Authors' contribution

Avi Peretz, Maya Azrad, Yish Levi and Motti Baum out most of the laboratory detections and wrote the manuscript. Assaf Rokney and Avi peretz conceived of the study and revised the manuscript. Maya Azrad and Motti Baum collected the data. Maya Azrad performed the statistical analysis. All authors read and approved the final manuscript.

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