

Activity of Tedizolid (TR-700) Against Well-characterized MRSA Strains of Diverse Epidemiological Origin

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Abstract

Background: TR-700 is a novel oxazolidinone reported to have potent activity against MRSA. To more fully explore its antistaphylococcal activity, TR-700 and 11 comparators were evaluated against 111 MRSA strains from 14 different epidemiologically characterized groups.

Methods: CLSI microdilution methodology was used to determine the MICs of TR-700, linezolid (LZD), trimethoprim/sulfamethoxazole (SXT), tigecycline (TGC), levofloxacin clindamycin, vancomycin (VA), daptomycin (DAP), oxacillin (OXA), erythromycin (ERY), gentamicin and ampicillin (PN). The strains were previously characterized isolates of: ST5-MRSA-II (USA100; n=10), ST36-MRSA-II (USA200/EMRSA16; n=10), ST8-MRSA-IV (USA300; n=10), ST1-MRSA-IV (USA400; n=10), ST8-MRSA-IV (USA500; n=10), ST45-MRSA-II (USA600; n=1), ST72-MRSA-IV (USA700; n=3), ST5-MRSA-IV (USA800; n=10), ST59-MRSA-IV (USA1000; n=3), ST30-MRSA-IV (USA1100; n=3), ST22-MRSA-IV (EMRSA15; n=10), ST80-MRSA-IV (n=10), ST247-MRSA-I (Iberian clone; n=11) and ST239-MRSA-III (Brazilian clone; n=10).

Results: TR-700, TGC and DAP were the most potent agents. TR-700 was 4-fold more potent than LZD. MICs of TR-700, LZD, and VA were unchanged against all epidemiological types, whereas TGC and DAP exhibited reduced potency against European community-associated ST80-MRSA-IV and ST239-MRSA-III (Brazilian clone) strains respectively. Except for OXA, PN and ERY, which were largely inactive, MICs of the other agents varied with strain type.

(Results summarized in table)

Conclusion: TR-700 was highly potent against all MRSA strain types and may prove to be effective against strains that are less susceptible or resistant to current anti-MRSA agents. Further studies with this agent are thus warranted.

Introduction

Tedizolid, formerly known as torezolid (TR-700), is a novel oxazolidinone with potent activity against MRSA. The current study was designed to extend previous investigations by comparing the antistaphylococcal activities of TR-700 and 11 comparators against 111 MRSA strains from 14 different epidemiologically characterized groups.

Methods

MICs were determined by CLSI microdilution methodology using Trek frozen microdilution panels containing torezolid, linezolid, trimethoprim/sulfamethoxazole, tigecycline, levofloxacin, clindamycin, vancomycin, daptomycin, oxacillin, erythromycin, gentamicin and ampicillin.

The isolates investigated were chosen to represent the below epidemiological groups. They were not random clinical isolates.

| | |
|----------------|-------------------------|
| ST5-MRSA-II | (USA100; n=10 isolates) |
| ST36-MRSA-II | (USA200/EMRSA16; n=10) |
| ST8-MRSA-IV | (USA300; n=10) |
| ST1-MRSA-IV | (USA400; n=10) |
| ST8-MRSA-IV | (USA500; n=10) |
| ST45-MRSA-II | (USA600; n=1) |
| ST72-MRSA-IV | (USA700; n=3) |
| ST5-MRSA-IV | (USA800; n=10) |
| ST59-MRSA-IV | (USA1000; n=3) |
| ST30-MRSA-IV | (USA1100; n=3) |
| ST22-MRSA-IV | (EMRSA15; n=10) |
| ST80-MRSA-IV | (n=10) |
| ST247-MRSA-I | (Iberian clone; n=11) |
| ST239-MRSA-III | (Brazilian clone; n=10) |

Results

The results in the table indicate that TR-700, tigecycline (MIC₉₀ 0.5 µg/ml) and daptomycin (MIC₉₀ ≤ 0.5 µg/ml) were the most potent agents against all types of MRSA. TR-700 was 4-fold more potent than the comparison oxazolidinone, linezolid. MICs of TR-700, linezolid and vancomycin were unchanged against all epidemiological types, whereas tigecycline and daptomycin exhibited reduced potency against the European community-associated ST80-MRSA-IV strains and the ST239-MRSA-III (Brazilian clone) strains respectively. In particular, 3 of 10 European community-associated ST80-MRSA-IV strains had elevated tigecycline MICs of ≥ 1 µg/ml, and 4 of 10 ST239-MRSA-III (Brazilian clone) strains had elevated daptomycin MICs of ≥ 1 µg/ml. The other epidemiological groups were more sensitive to tigecycline and daptomycin. The narrow MIC range of TR-700 (0.12 - 0.5 µg/ml) indicated that its activity was not compromised by the resistance mechanisms of this diverse collection of MRSA strains.

Except for oxacillin, ampicillin and erythromycin which were inactive, MICs of the other agents varied with the different strain types. Specifically, activity of trimethoprim/sulfamethoxazole was compromised against ST8-MRSA-IV (USA500) and ST239-MRSA-III (Brazilian clone) strains. Levofloxacin was compromised against ST8-MRSA-IV (USA500), ST22-MRSA-IV (EMRSA15), ST247-MRSA-I (Iberian clone) and ST239-MRSA-III (Brazilian clone) strains. Erythromycin was inactive against most strains but was active against some ST22-MRSA-IV (EMRSA15) strains. Clindamycin was compromised against ST5-MRSA-II (USA100), ST36-MRSA-II (USA200/EMRSA16), ST8-MRSA-IV (USA500), ST247-MRSA-I (Iberian clone) and some ST239-MRSA-III (Brazilian clone) strains. Gentamicin was compromised against ST247-MRSA-I (Iberian clone) and ST239-MRSA-III (Brazilian clone) strains and was variable against ST8-MRSA-IV (USA500) strains.

Table

| Table. Activity Against MRSA in µg/ml | | | |
|---------------------------------------|-------------------|-------------------|-------------------|
| Drug | MIC Range | MIC ₅₀ | MIC ₉₀ |
| Tedizolid | 0.12 - 0.5 | 0.5 | 0.5 |
| Linezolid | 0.5 - 4 | 2 | 2 |
| Trimethoprim/sulfa | ≤ 0.5/9.5 - >2/38 | ≤ 0.5/9.5 | >2/38 |
| Tigecycline | 0.06 - >1 | 0.25 | 0.5 |
| Levofloxacin | 0.12 - >4 | 4 | >4 |
| Clindamycin | 0.06 - >16 | 0.12 | >16 |
| Vancomycin | ≤ 0.25 - 4 | 0.5 | 1 |
| Daptomycin | ≤ 0.5 - 2 | ≤ 0.5 | ≤ 0.5 |
| Oxacillin | 0.12 - >4 | >4 | >4 |
| Erythromycin | 0.12 - >8 | >8 | >8 |
| Gentamicin | ≤ 0.06 - >16 | 0.25 | >16 |
| Ampicillin | 1 - >8 | >8 | >8 |

Conclusion

TR-700 was highly potent against all MRSA strain types, including those with reduced susceptibility to daptomycin and tigecycline. TR-700 shows potential as a therapeutic agent against strains that are less susceptible or resistant to currently available anti-MRSA agents. Further studies are thus warranted.