

In vitro evaluation of AZD2563, a new oxazolidinone, tested against unusual Gram-positive species

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Revised abstract

Background: The recently introduced oxazolidinone, linezolid (LZD), has a spectrum and potency directed against Gram-positive (G+) organisms, including antimicrobial-resistant isolates (drug-resistant *S. pneumoniae*, VRE, MRSA and MR-CoNS). The newest agent in this class, AZD2563 was tested against uncommonly isolated G+ species to establish complete spectrum of coverage.

Methods: By NCCLS broth microdilution methods, 120 strains were tested (48 *Corynebacterium* spp., 10 species; 27 *Listeria* spp., 2 species; 11 *Micrococcus* spp., 2 species; 23 *Bacillus* spp., 3 species; 6 *Stomatococcus mucilaginosus* and 1 strain each of 5 other species) against AZD2563 and compared to LZD, quinupristin-dalfopristin (Q-D), vancomycin (VAN), penicillin (PEN), clindamycin (CLI), erythromycin (ERY), levofloxacin (LEVX) and gentamicin (GEN).

Results: ERY and CLI were generally less active against this organism group (ave., 65 and 46% susceptibility [S], respectively). VAN and Q-D inhibited all but 1 isolate of *Bacillus* spp., and LEVX was least active versus *Corynebacterium* spp. and *S. mucilaginosus* (33 to 67% S). The AZD2563/LZD MIC₅₀; % inhibited at ≤4 µg/mL were: for corynebacteria (0.25/0.25 µg/mL; 100/100%), *Listeria* spp. (2/2 µg/mL; 100/100%), *Micrococcus* spp. (1/1 µg/mL; 100/100%), *Bacillus* spp. (0.5/1 µg/mL; 100/100%), and *S. mucilaginosus* (0.5/1 µg/mL; 100/100%). Using the MIC₉₀ values, AZD2563 was slightly more potent than LZD (two-fold). Only 4 species groups had AZD2563 MICs at 2 µg/mL (*Aerococcus*, *Leuconostoc*, *Listeria*, *Rhodococcus*), all other strains were ≤ 1 µg/mL.

Conclusions: The AZD2563 potency and spectrum versus these species was complete including some strains resistant to penicillins, macrolides-lincosamides, and fluoroquinolones. These data complement reports of high AZD2563 activity against all enterococci, staphylococci and streptococci; and encourage advanced clinical development.

Introduction

- Resistance to antimicrobial agents among commonly isolated Gram-positive species has been increasing in recent years, most notably by the penicillin-resistant *Streptococcus pneumoniae*, glycopeptide-resistant enterococci (usually *E. faecium*), macrolide-resistant streptococci of many species, and methicillin-resistant staphylococci.
- In addition, less frequently identified Gram-positive species have acquired resistance to various agents, with some of these organisms assuming greater clinical significance among immunocompromised hosts.
- To address these threats to infection chemotherapy, novel agents have been rapidly brought into clinical development, such as the everninomicins (evernamycin), streptogramin combinations (Q-D), fluoroquinolones (gatifloxacin, gemifloxacin, moxifloxacin), glycopeptides (daptomycin, BI397, LY333328), and oxazolidinones (LZD). AZD2563 joins LZD as a promising new oxazolidinone with activity targeted against Gram-positive organisms.
- This report summarizes the *in vitro* spectrum of AZD2563, tested by reference methods, against recent clinical isolates of very unusual Gram-positive species.

Methods

Organisms tested

- Recent clinical isolates derived from the collection of JMI Laboratories (North Liberty, IA) were tested against AZD2563 and various drug-class representatives including LZD, fluoroquinolones, macrolide-lincosamide-streptogramins, aminoglycosides, penicillins, and glycopeptides.
- The organisms tested were: *Corynebacterium* spp. (10 species; 48 strains), *Listeria* spp. (2 species; 27 strains), *Micrococcus* spp. (2 species; 11 strains), *Bacillus* spp. (3 species; 23 strains), *Stomatococcus mucilaginosus* (6 strains) and 1 strain each of *Aerococcus* spp., *Dermabacter hominis*, *Lactococcus cremori*, *Leuconostoc* spp. and *Rhodococcus equi*.
- Organisms were frozen at -80°C until subcultured and processed.

Susceptibility tests

- All tests were performed in Mueller–Hinton broth by the NCCLS (2000) reference broth microdilution method, using trays prepared by TREK Diagnostics (Westlake, OH) stored frozen at -80°C.
- AZD2563 was provided by AstraZeneca (Macclesfield, UK) and all other antimicrobials were obtained from US manufacturers.
- Quality assurance was monitored by NCCLS control strains: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619. All quality control results were observed to be within published NCCLS limits or those provided by antimicrobial manufacturers.

Results

Table 1. Activity of AZD2563 tested against 115 strains of unusual Gram-positive isolates (µg/mL).

Organism/antimicrobial (no. tested)	MIC ₅₀	MIC ₉₀	Range	% susceptible ^a
<i>Corynebacterium</i> spp. (48)				
AZD2563	0.25	0.25	0.03–0.5	100.0 ^b
LZD	0.25	0.5	0.12–1	100.0
VAN	0.5	0.5	0.12–0.5	100.0
Q-D	0.12	0.5	0.03–1	100.0
PEN	8	>8	0.03–>8	12.5
ERY	4	>16	0.05–>16	12.5
CLI	>4	>4	≤ 0.5–>4	8.3
LEVX	8	>8	0.06–>8	33.3
GEN	0.5	>8	≤ 0.25–>8	62.5
<i>Listeria</i> spp. (27)				
AZD2563	2	2	1–2	100.0 ^b
LZD	2	2	2	100.0
VAN	0.5	1	0.5–1	100.0
Q-D	1	1	1	100.0
PEN	0.5	1	0.12–1	4.0
ERY	0.25	0.25	0.12–0.25	100.0
CLI	1	2	≤ 0.5–2	12.0
LEVX	1	1	0.5–1	100.0
GEN	≤ 0.25	≤ 0.25	≤ 0.25	100.0
<i>Micrococcus</i> spp. (11)				
AZD2563	0.5	1	0.5–1	100.0 ^b
LZD	1	1	0.5–1	100.0
VAN	0.12	0.5	0.12–1	100.0
Q-D	0.06	0.12	0.06–0.25	100.0
PEN	0.12	0.25	≤ 0.004–8	72.7
ERY	0.25	8	0.015–16	54.5
CLI	≤ 0.5	1	≤ 0.5–1	81.7
LEVX	1	2	0.5–4	90.9
GEN	≤ 0.25	0.5	≤ 0.25–0.5	100.0
<i>Bacillus</i> spp. (23)				
AZD2563	0.5	1	0.12–1	100.0 ^b
LZD	1	1	0.25–1	100.0
VAN	1	1	0.06–32	95.6
Q-D	1	1	0.25–4	95.6
Oxacillin	16	>16	0.12–>16	34.8
ERY	0.25	>16	≤ 0.12–>16	65.2
CLI	1	>4	≤ 0.5–>4	43.5
LEVX	0.12	0.25	0.03–4	95.6
GEN	≤ 0.25	0.5	≤ 0.25–1	100.0
<i>Stomatococcus</i> spp. (6)				
AZD2563	0.5	-	0.25–0.5	100.0 ^b
LZD	1	-	0.5–1	100.0
VAN	0.5	-	0.5–1	100.0
Q-D	0.12	-	0.06–0.5	100.0
PEN	0.06	-	0.015–8	66.7
ERY	0.03	-	≤ 0.008–>16	83.3
CLI	≤ 0.5	-	≤ 0.5–>4	66.7
LEVX	1	-	0.25–8	66.7
GEN	1	-	≤ 0.25–>8	83.3

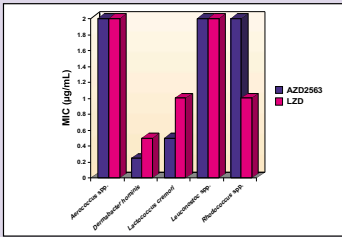
^aSusceptibility categories of the NCCLS (2001) as applied to staphylococci.

^bValues based on ≤ 2 µg/mL as no standard yet defined.

- Table 1 lists MIC results for AZD2563 and comparators for those species having ≥ 6 isolates. The AZD2563 MIC₉₀ ranged from 0.25 µg/mL (*Corynebacterium* spp.) to 2 µg/mL (*Listeria* spp.). This potency was slightly superior to LZD, but neither oxazolidinone had an MIC > 2 µg/mL.

- Generally, the oxazolidinones, Q-D, and VAN achieved a complete spectrum of activity against these species (Table 1), whereas marked variations in spectra were noted for the other agents.

Fig 1. Activity of AZD2563 and LZD versus single strains of uncommonly isolated species.



- Fig 1 shows the potency of both oxazolidinones against five further species. Both agents were effective, with MIC ranges of 0.25–2 µg/mL.

Table 2. Comparisons of broth microdilution MICs to those of the agar dilution method (NCCLS)* for the two oxazolidinones tested against 120 isolates of Gram-positive cocci.

Antimicrobial/organism (no. tested)	Broth/agar dilution MIC ratio				
	≤ 0.25	0.5	1	2	≥ 4
AZD2563					
<i>S. pneumoniae</i> (30)	0	0	30	0	0
Other streptococci (30)	0	13	17	0	0
Staphylococci (30)	0	0	30	0	0
Enterococci (30)	0	0	30	0	0
Total (120) [†]	0	13	107	0	0
LZD					
<i>S. pneumoniae</i> (30)	0	0	29	1	0
Other streptococci (30)	0	15	12	3	0
Staphylococci (30)	0	0	30	0	0
Enterococci (30)	0	0	30	0	0
Total (120) [†]	0	15	101	4	0

*Testing was by reference NCCLS methods.

[†]All of the AZD2563 results were within the ± one log₂ dilution range and 89.2% were at a ratio of 1.

All of the control LZD results were within the ± one log₂ dilution range and 84.2% were at a ratio of 1.

- Results obtained using NCCLS reference agar and broth dilution methods were very similar. Table 2 illustrates the variation in oxazolidinone MICs with each dilution method against 120 strains of Gram-positive cocci from four organism groups. A total of 84.2–89.2% of agar and broth results were identical (ratio of 1).

Conclusions

- AZD2563 and LZD exhibited similar activity versus unusual Gram-positive cocci and bacilli with all MIC values at ≤ 2 µg/mL.
- The following genera/species were considered susceptible to AZD2563: *Aerococcus* spp., *Bacillus* spp., *Corynebacterium* spp., *D. hominis*, *L. cremori*, *Leuconostoc* spp., *Listeria* spp., *Micrococcus* spp., *R. equi* and *S. mucilaginosus*.
- The breadth of the AZD2563 spectrum against Gram-positive species should provide a promising alternative for the treatment of infections caused by organisms including those resistant to other antimicrobial classes.

Selected references

1. Bryskier A. (2000) *Clin Infect Dis*;31:1423–1466.

2. Diekema DJ & Jones RN. The oxazolidinones: promising agents for Gram-positive infections? (2001) *Lancet*, *in press*.