

Activity of AZD2563 and Comparator Agents Tested Against 6,444 Staphylococci, Streptococci and Enterococci (North America, 2001 - 2002)

The JONES Group/JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

TR FRITSCH, TR ANDEREGG, RN JONES
The JONES Group/JMI Laboratories, North Liberty, IA

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AMENDED ABSTRACT

Background: AZD2563 (AZD) is a long-acting oxazolidinone currently in pre-clinical development that inhibits protein synthesis of Gram-positive (GP) organisms by binding to the 50S ribosomal subunit. We evaluated the contemporary (2001 - 2002) in vitro activity of AZD and comparator agents against a collection of 6,444 GP strains originating from medical centers in North America.

Methods: The tested organisms included *S. aureus* (3,607 strains, 40.4% oxacillin [OXA]-resistant [R]), coagulase-negative staphylococci (CoNS; 840, 76.5% OXA-R), *S. pneumoniae* (SPN; 429, 22% penicillin non-susceptible [S]), other streptococci (598) and enterococci (ENT; 970, 21% vancomycin [VAN]-R). The strains were tested against AZD, linezolid (LZD), quinupristin/dalfopristin (Q/D), levofloxacin (LEV) and > 20 other agents by the NCCLS broth microdilution method (M7-A6).

Results: The results follow in the table:

Organism (no. tested)	MIC _{50/90} in µg/ml (% S)				
	AZD*	LZD	VAN	Q/D	LEV
S. aureus OXA-S (2,148)	1/2 (100.0)	2/2 (100.0)	1/1 (100.0)	0.25/0.5 (>99.9)	0.12/0.5 (92.6)
OXA-R (1,459)	1/2 (99.9)	2/2 (99.9)	0.25/2 (100.0)	0.5/0.5 (100.0)	>4/>4 (8.6)
CoNS OXA-S (197)	1/1 (100.0)	1/1 (100.0)	1/2 (100.0)	0.25/0.25 (100.0)	0.25/4 (88.3)
OXA-R (643)	1/1 (99.8)	1/1 (99.8)	2/2 (100.0)	0.25/0.5 (99.7)	4/>4 (43.4)
SPN (429)	1/1 (100.0)	1/2 (100.0)	0.25/0.5 (100.0)	0.5/0.5 (100.0)	1/1 (99.7)
ENT VAN-S (800)	2/2 (99.6)	2/2 (99.6)	-	8/>8 (9.9)	2/>4 (53.1)
VAN-R (170)	1/2 (98.8)	2/2 (98.8)	-	1/4 (84.1)	>4/>4 (2.9)

*Breakpoint applied ≤ 2 µg/ml (similar or two-fold lower than LZD).

Documented oxazolidinone-R strains (5 isolates) with AZD and LZD MICs at ≥ 8 µg/ml were identified as having a ribosomal G2576U mutation.

Conclusions: AZD was highly active against all GP species tested with MIC_{50/90} results ranging from 1 to 2 µg/ml. The distribution of MIC values were very similar to those of linezolid, with the exception of a two-fold lower MIC for *S. aureus* (MIC₅₀), VRE (MIC₅₀), and *S. pneumoniae* (MIC₉₀). All isolates that were R to linezolid were also AZD-R. AZD activity against GP organisms was comparable to LZD and should be a useful alternative for treatment of emerging R GP infections.

INTRODUCTION

The resistance profiles of Gram-positive organisms have been undergoing a profound shift during the past 10 years, necessitating the identification and clinical development of novel compounds such as the evernimomycins, streptogramin combinations, fluoroquinolones, glycopeptides and oxazolidinones. AZD2563 is a new oxazolidinone that features a novel C-5 side-chain substitution and joins linezolid as a promising once daily oral and parenteral oxazolidinone agent with activity targeting a broad range of Gram-positive organisms. AZD2563 may have some potency and half-life advantages over previously studied oxazolidinone compounds.

The oxazolidinones inhibit protein synthesis by preventing the formation of the ribosomal 70S initiation complex and are considered to be bacteriostatic. Despite the rare occurrence of resistance that has been reported with linezolid, this family of compounds remains a viable therapeutic alternative for methicillin-resistant staphylococci, penicillin-resistant streptococci and vancomycin-resistant enterococci. They also demonstrate activity against less commonly isolated organisms such as *Bacillus*, *Corynebacterium* and *Listeria* species.

The present study examines the activity of AZD2563 and other comparator agents against a large collection of contemporary isolates of staphylococci, streptococci and enterococci originating from medical centers in North America.

MATERIALS & METHODS

Specimen Collection. A total of 6,444 strains of Gram-positive cocci originating from 34 medical centers in North America (2001-2002) were included in the study and were recovered consecutively from patients hospitalized with bacteremia, pneumonia, skin and soft tissue infections, and urinary tract infections. Isolates were identified by the submitting laboratory and confirmed by the monitoring facility (The JONES Group/JMI Laboratories). The collection consisted of *S. aureus* (3607 strains; 40.4% resistant to oxacillin), coagulase-negative staphylococci (CoNS; 840 strains; 76.5% resistant to oxacillin), *S. pneumoniae* (429 strains; 22% penicillin non-susceptible), β -haemolytic streptococci (483 strains), viridans group streptococci (115 strains), and enterococci (970 strains; 17.5% resistant to vancomycin).

Susceptibility Testing. All strains were tested by the NCCLS reference broth microdilution method in Mueller-Hinton broth (with 2 - 5% lysed horse blood added for testing of streptococci) against AZD2563 and comparator agents representing the most common classes and examples of drugs used for the empiric or directed treatment of infections caused by the Gram-positive organisms. Interpretation of quantitative MIC results was in accordance with NCCLS methods and criteria, except for AZD2563, for which the susceptibility breakpoint has not yet been defined. For comparative purposes, a breakpoint was chosen at ≤ 2 µg/ml (same as linezolid for enterococci and streptococci, and two-fold lower than for staphylococci e.g. ≤ 4 µg/ml). Quality control strains utilized included *S. aureus* ATCC 29213, *Streptococcus pneumoniae* ATCC 49619 and *Enterococcus faecalis* ATCC 29212.

RESULTS

- The Gram-positive pathogens most frequently isolated in North America during this study (2001-2002) were: *S. aureus* (3,607 isolates, 60%); CoNS (840 isolates, 13%); enterococci (970 isolates, 15%); β -haemolytic streptococci (483 isolates, 7.5%), *S. pneumoniae* (429 isolates, 6.6%) and viridans group streptococci (115 isolates, 1.8%).
- With the exception of 6 isolates (0.09%) demonstrating resistance (≥ 8 µg/ml) to linezolid and AZD2563 (1 each *S. aureus* [oxacillin-resistant], CoNS [oxacillin-resistant], viridans-group streptococcus and enterococcus [vancomycin-resistant]; and 2 enterococci [vancomycin-susceptible]), all MIC_{50/90} results for the remaining 6,438 isolates for both compounds ranged from 1 to 2 µg/ml.
- All AZD2563- and linezolid-resistant isolates were found to have the G2576U ribosomal mutation that has been recently described as the mechanism of resistance.
- No differences were noted for AZD2563 MIC_{50/90} results between oxacillin-susceptible and -resistant staphylococci, and only one log₂ dilution separated penicillin-nonsusceptible (MIC₉₀, 2 µg/ml) pneumococci from penicillin-susceptible (MIC₉₀, 1 µg/ml) strains.
- With the exception of one (0.86%) AZD2563- and linezolid-resistant viridans group streptococcal isolate, the oxazolidinones remained highly active against this group and the β -haemolytic streptococci with a MIC_{50/90} of 1 µg/ml.
- AZD2563 was the most active compound of those tested against vancomycin-susceptible and -resistant enterococci (MIC₉₀ 2 µg/ml).

RESULTS

Table 1. In vitro activity of AZD2563 and comparator agents tested against 6,444 staphylococci, streptococci and enterococci originating from medical centers in North America (2001 - 2002).

Organism/antimicrobial agent (no. tested)	MIC (µg/ml)			% by category:	
	50%	90%	Range	Susceptible	Resistant
S. aureus					
Oxacillin-susceptible (2,148)					
AZD2563	1	2	≤ 0.06 -4	100.0 ^a	<0.1
Linezolid	2	2	0.25-4	100.0	<0.1
Quinupristin/Dalfopristin	0.25	0.5	≤ 0.06 -2	>99.9	0.0
Vancomycin	1	1	0.25-2	100.0	0.0
Penicillin	8	32	≤ 0.015 ->32	16.7	83.3
Erythromycin	0.25	>8	≤ 0.06 ->8	75.3	23.7
Clindamycin	0.12	0.12	≤ 0.06 ->8	94.6	5.2
Levofloxacin	0.12	0.5	≤ 0.03 ->4	92.6	5.4
S. aureus					
Oxacillin-resistant (1,459)					
AZD2563	1	2	≤ 0.06 ->8	99.9 ^a	<0.1
Linezolid	2	2	≤ 0.25 -16	99.9	<0.1
Quinupristin/Dalfopristin	0.5	0.5	≤ 0.06 -1	100.0	0.0
Vancomycin	0.25	2	0.25-2	100.0	0.0
Erythromycin	>8	>8	≤ 0.06 ->8	3.8	96.0
Clindamycin	>8	>8	≤ 0.06 ->8	25.3	74.6
Levofloxacin	>4	>4	0.06->4	8.6	74.4
Coagulase-neg. staphylococci					
Oxacillin-susceptible (197)					
AZD2563	1	1	≤ 0.06 -2	100.0 ^a	<0.1
Linezolid	1	1	≤ 0.06 -2	100.0	<0.1
Quinupristin/Dalfopristin	0.25	0.25	≤ 0.06 -1	100.0	0.0
Vancomycin	1	2	≤ 0.12 -2	100.0	0.0
Erythromycin	0.25	>8	≤ 0.06 ->8	61.4	37.0
Clindamycin	≤ 0.06	0.25	≤ 0.06 ->8	90.9	9.1
Levofloxacin	0.25	4	0.06->4	88.3	9.1
Coagulase-neg. staphylococci					
Oxacillin-resistant (643)					
AZD2563	1	1	0.12->8	99.8 ^a	<0.1
Linezolid	1	1	0.12->8	99.8	<0.1
Quinupristin/Dalfopristin	0.25	0.5	≤ 0.06 -2	99.7	0.0
Vancomycin	2	2	≤ 0.12 -4	100.0	0.0
Erythromycin	>8	>8	≤ 0.06 ->8	17.0	82.6
Clindamycin	>8	>8	≤ 0.06 ->8	48.4	51.1
Levofloxacin	4	>4	0.06->4	43.4	43.1
S. pneumoniae					
Penicillin-susceptible (333)					
AZD2563	1	1	≤ 0.06 -2	100.0 ^a	<0.1
Linezolid	1	2	≤ 0.06 -2	100.0	<0.1
Quinupristin/Dalfopristin	0.5	0.5	0.12-1	100.0	0.0
Vancomycin	0.25	0.5	≤ 0.12 -1	100.0	<0.1
Erythromycin	≤ 0.06	≤ 0.06	≤ 0.06 ->8	93.1	6.3
Clindamycin	≤ 0.06	≤ 0.06	≤ 0.06 ->8	97.6	2.1
Levofloxacin	1	1	0.25-4	99.7	0.0
S. pneumoniae					
Penicillin-non-susceptible (96)					
AZD2563	1	2	0.25-2	100.0 ^a	<0.1
Linezolid	1	2	0.25-2	100.0	<0.1
Quinupristin/Dalfopristin	0.5	0.5	0.12-1	100.0	0.0
Vancomycin	0.25	0.5	≤ 0.12 -0.5	100.0	<0.1
Erythromycin	2	>8	≤ 0.06 ->8	38.5	60.4
Clindamycin	≤ 0.06	>8	≤ 0.06 ->8	52.1	18.7
Levofloxacin	1	1	0.5->4	99.0	1.0
β-haemolytic streptococci (483)					
AZD2563	1	1	≤ 0.06 -2	100.0 ^a	<0.1
Linezolid	1	1	≤ 0.06 -2	100.0	<0.1
Quinupristin/Dalfopristin	0.25	0.5	≤ 0.06 -1	100.0	0.0
Vancomycin	0.5	0.5	≤ 0.12 -1	100.0	0.0
Penicillin	≤ 0.015	0.06	≤ 0.015 -0.12	100.0	0.0
Erythromycin	≤ 0.06	2	≤ 0.06 ->8	81.4	18.4
Clindamycin	≤ 0.06	≤ 0.06	≤ 0.06 ->8	93.8	6.2
Levofloxacin	0.5	1	≤ 0.03 ->4	99.4	0.4

Table 1. Continued.

Organism/antimicrobial agent (no. tested)	MIC (µg/ml)			% by category:	
	50%	90%	Range	Susceptible	Resistant
viridans gr. streptococci (115)					
AZD2563	1	1	≤ 0.06 ->8	99.1 ^a	<0.1
Linezolid	1	1	0.12-8	99.1	<0.1
Quinupristin/Dalfopristin	0.5	1	≤ 0.06 -1	100.0	0.0
Vancomycin	0.5	1	≤ 0.12 -1	100.0	0.0
Penicillin	0.06	2	≤ 0.015 -8	75.7	4.3
Erythromycin	≤ 0.06	8	≤ 0.06 ->8	54.8	43.5
Clindamycin	≤ 0.06	≤ 0.06	≤ 0.06 ->8	93.0	7.0
Levofloxacin	1	2	≤ 0.06 ->4	94.8	3.5
Enterococcus spp.					
Vancomycin-susceptible (800)					
AZD2563	2	2	≤ 0.06 ->8	99.6 ^a	<0.1
Linezolid	2	2	0.25->8	99.6	0.2
Quinupristin/Dalfopristin	8	>8	0.25->8	9.9	68.7
Penicillin	4	16	0.03->32	89.7	10.3
Erythromycin	>8	>8	≤ 0.06 ->8	10.1	56.1
Levofloxacin	2	>4	≤ 0.03 ->4	53.1	45.5
Enterococcus spp.					
Vancomycin-resistant (170)					
AZD2563	1	2	≤ 0.06 ->8	98.8 ^a	<0.1
Linezolid	2	2	0.5->8	98.8	0.6
Quinupristin/Dalfopristin	1	4	0.25->8	84.1	11.7
Penicillin	>32	>32	0.5->32	10.6	89.4
Erythromycin	>8	>8	1->8	0.0	90.6
Levofloxacin	>4	>4	1->4	2.9	97.1

a. A susceptible breakpoint equal to linezolid (NCCLS, 2003) was used for comparative purposes only.

b. No breakpoint has been established by the NCCLS.

CONCLUSIONS

- AZD2563 was highly active against all Gram-positive species tested with MIC_{50/90} results ranging from 1 to 2 µg/ml.
- Distribution of MIC values was very similar to those of linezolid, with the exception of a two-fold lower MIC for *S. aureus* (MIC₅₀), VRE (MIC₅₀) and *S. pneumoniae* (MIC₉₀).
- All isolates (6) that were resistant to linezolid were also resistant (MIC, ≥ 8 µg/ml) to AZD2563, and were documented to have a ribosomal G2576U mutation.
- AZD2563 potency was not affected by oxacillin resistance among staphylococci, penicillin resistance among streptococci nor vancomycin resistance among enterococci.
- AZD2563 activity against staphylococci, streptococci and enterococci was comparable to that of linezolid and the new oxazolidinone should be a useful alternative for treatment of emerging resistant Gram-positive infections.

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