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Activity of AZD2563, a new oxazolidinone, tested against Gram-positive cocci collected in Latin American medical centers in 2001

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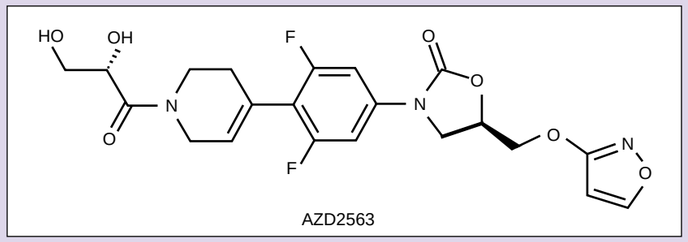
Introduction

- Oxazolidinones inhibit protein synthesis by acting against the formation of the ribosomal 70S initiation complex and are generally considered to be bacteriostatic. The first oxazolidinone to be licensed for clinical use was linezolid.
- Multicenter and focused in-vitro studies have proven linezolid to be a valuable therapeutic option against Gram-positive cocci, particularly against multidrug-resistant isolates. Oxazolidinones have also demonstrated activity against less commonly isolated Gram-positive organisms, such as *Bacillus* spp., *Corynebacterium* spp., and *Listeria* spp.
- AZD2563 is a new oxazolidinone that has a C-5 substitution with O- or N-linked, five- and six-member aromatic heterocycles (Figure 1).[1]

Figure 1. Chemical structure of AZD2563



AZD2563

- This study examines the comparative potency of AZD2563 tested against clinical isolates of aerobic Gram-positive cocci isolated from patients hospitalized in Latin American medical centers during 2001.

Methods

- Aerobic Gram-positive cocci were collected in ten Latin American laboratories distributed throughout five countries: Sao Paulo, Florianopolis, Porto Alegre and Brasília in Brazil; Buenos Aires and San Isidro in Argentina; Santiago (two centers), Chile; Caracas, Venezuela; and Mexico City, Mexico. The selection of participant centers was based on the principle that they should be sentinel in their respective geographic region.
- The participant medical centers were required by protocol to collect isolates from consecutive patients from specific sites of infections. The isolates were collected from patients hospitalized with bacteremia, pneumonias, skin and soft tissue infection, and urinary tract infection (January to December 2001).
- Antimicrobial susceptibility testing was performed using broth microdilution methods as described by the National Committee for Clinical Laboratory Standards (NCCLS).[2] Antimicrobial agents were obtained from their respective manufacturers as laboratory grade powder, and included AZD2563, linezolid, oxacillin, ciprofloxacin, gatifloxacin, quinupristin/dalfopristin, teicoplanin and vancomycin.
- Quality control strains utilized were *Streptococcus pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853.
- Breakpoint interpretive criteria used were those established by the NCCLS.[2] A tentative susceptibility breakpoint of ≤4 µg/ml was applied for AZD2563[3] for comparison purposes only.

Results

- The Gram-positive microorganism most frequently isolated during the period of the study was *S. aureus* (196 strains, 63.0%), followed by coagulase-negative staphylococci (CoNS) (77 strains, 24.8%) and *Enterococcus* spp. (38 strains, 12.2%).
- AZD2563 (MIC_{50}, 1 µg/ml) and linezolid (MIC_{50}, 2 µg/ml) were the only compounds active against all of the strains tested (Table 1).

Table 1. Antimicrobial activity and spectrum of AZD2563, linezolid and selected other antimicrobial agents against all Gram-positive cocci

	All isolates (311)			
Antimicrobial agents	**MIC_{50} (µg/ml)**	**MIC_{90} (µg/ml)**	**% susceptible**	**% resistant**
AZD2563	1	2	100.0	0.0
Linezolid	2	2	100.0	0.0
Oxacillin[a]	8	>32	47.6[a]	52.4[a]
Gatifloxacin	0.25	4	85.9	5.5
Quinupristin/dalfopristin	0.25	4	88.7	10.9
Teicoplanin	0.5	2	98.1	0.3
Vancomycin	1	2	99.7	0.3

[a] Includes only staphylococci (196 *S. aureus* and 77 CoNS).

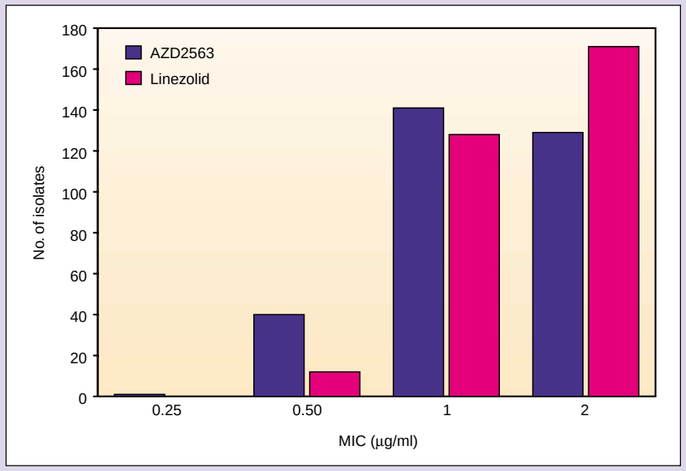
Table 2. Antimicrobial activity and spectrum of AZD2563, linezolid and selected other antimicrobial agents used to treat Gram-positive infections

	Pathogen (no. tested)					
	***S. aureus* (196)**		**CoNS (77)**		***Enterococcus* spp. (38)**	
Antimicrobial agents	**$MIC_{50/90}$**	**% S**	**$MIC_{50/90}$**	**% S**	**$MIC_{50/90}$**	**% S**
AZD2563	1/2	100.0	1/1	100.0	2/2	100.0
Linezolid	2/2	100.0	2/2	100.0	2/2	100.0
Oxacillin	0.5/>8	56.1	>8/>8	26.0	>8/>8	NA[a]
Ciprofloxacin	1/>4	58.7	0.5/>4	62.3	1/>2	55.3
Gatifloxacin	0.12/4	88.3	0.12/2	89.6	0.5/>4	65.8
Quinupristin/dalfopristin	0.25/0.5	100.0	0.25/0.5	98.9	8/>8	5.3
Teicoplanin	0.5/1	100.0	2/8	93.5	0.12/0.25	97.4
Vancomycin	1/1	100.0	1/2	100.0	1/2	97.4

[a] NA: Not applicable. There are no breakpoints defined by NCCLS.[2] S=susceptible

- AZD2563 was more potent than linezolid, especially against staphylococci (Table 1, 2, and Figure 2).
- Only one isolate (*Enterococcus* spp.) was resistant to vancomycin or teicoplanin (0.3% resistance overall) (Table 2).
- All staphylococci were susceptible to vancomycin, but decreased susceptibility to teicoplanin was detected among CoNS (MIC_{90}, 8 µg/ml; 93.5% susceptibility; Table 2).
- Quinupristin/dalfopristin was highly active against *S. aureus* (MIC_{90}, 0.5 µg/ml; 100.0% susceptibility) and CoNS (MIC_{90}, 0.5 µg/ml; 98.9% susceptibility). However, most enterococci isolates were resistant to this compound (MIC_{90}, >8 µg/ml; 5.3% susceptibility); most of these enterococci isolates were *E. faecalis* (Table 2).

Figure 2. Distribution of MICs of AZD2563 and linezolid against 311 clinical strains of Gram-positive isolates collected in Latin American medical centers



Conclusions

- The excellent in-vitro activity demonstrated in the present study coupled with early favorable PK/PD features[4] established in other studies indicate that AZD2563 has potential for treating infections caused by Gram-positive cocci.

References

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