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Susceptibility of *Gardnerella vaginalis* to Solithromycin (CEM-101)

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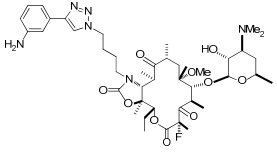
Abstract

Background: Solithromycin (CEM-101), a new macrolide and the first fluoroketolide, is in Phase 3 development for CABP and gonococcal urethritis. It has shown to be efficacious and safe in Phase 2 trials in these indications when used as monotherapy. In addition to activity against *Neisseria gonorrhoeae*, solithromycin also has demonstrated activity against *Chlamydia trachomatis* and *Mycoplasma genitalium* in urethritis. *Gardnerella vaginalis* is implicated in bacterial vaginosis and is also associated with non-gonococcal urethritis in men and women. The objective of this study was to determine the in vitro susceptibility of *Gardnerella vaginalis* to solithromycin.

Methods: MICs of solithromycin and comparator drugs were determined for 21 clinical strains of *Gardnerella vaginalis* cultured from vaginal specimens collected in 2012 from patients and submitted to the Clinical Microbiology Laboratories at the University of Rochester Medical Center, Rochester, NY. MICs were determined by broth microdilution methodology in cation-adjusted Mueller-Hinton broth supplemented with 2.5% lysed horse blood as recommended by CLSI M7-A8. Microdilution trays were incubated for 72 hours at 36° C in ambient air supplemented with 5% CO_2. The range of MICs, MIC_{50}s and MIC_{90}s of all drugs were determined.

Results: The MIC range and MIC_{90} of solithromycin for *Gardnerella vaginalis* were ≤0.002-0.12 µg/ml and 0.12 µg/ml. The MIC_{90}s of clindamycin, azithromycin, doxycycline and metronidazole were 0.12, 8.0, 2.0 and 64 µg/ml, respectively.

Conclusion: Solithromycin was more active than metronidazole and equal to clindamycin against *Gardnerella vaginalis*. Solithromycin could provide broader coverage than metronidazole and clindamycin for organisms implicated in bacterial urethritis. In addition to covering gonococcus, chlamydia and mycoplasma, solithromycin could also cover *Gardnerella vaginalis* in bacterial urethritis. Solithromycin may also be useful in treating bacterial vaginosis caused by *Gardnerella vaginalis*.



Solithromycin

Introduction

Solithromycin (CEM-101, SOLI) is in a multinational Phase 3 clinical trial for treatment of bacterial urethritis caused by gonococcus and chlamydia, where it is being tested as monotherapy against the comparator intramuscular ceftriaxone plus oral azithromycin, in addition to two global trials for community-acquired bacterial pneumonia (CABP). SOLI demonstrated 100% efficacy in all clinically proven gonorrhea cases in a Phase 2 study (1). SOLI has also shown to be active against *Mycoplasma genitalium* (2). *Gardnerella vaginalis* can cause urethritis and vaginitis and is also found in urinary tract infections (3, 4). In some cases, *G. vaginalis* can be the single infecting pathogen, but it can also be a co-infecting pathogen. The ability to treat bacterial vaginosis can be complicated by biofilm formation (5). SOLI has been demonstrated to have activity against biofilms (6). SOLI was tested against *G. vaginalis* to determine if it would provide coverage against *G. vaginalis* in vaginitis and urethritis.

Materials and Methods

Drugs. MICs of the following drugs were determined: azithromycin (USP, Lot# G; Sigma, Lot# E446421/1v), cefixime (USP, Lot# F), ceftriaxone (Sigma, Lot# 091M0741v), clarithromycin (USP, Lot# GIG324), clindamycin (Sigma, Lot# 021M1533v), doxycycline (Sigma, Lot# BCBF9827V), metronidazole (Sigma, Lot# 095K0693), penicillin (Sigma, Lot# BCBF3866V), and solithromycin (Cempra, Lot# EKS11646). Drugs were dissolved and diluted for testing per recommendations in CLSI M100-S22.

Organisms. Clinical strains were cultured from patient specimens submitted to the Clinical Microbiology Laboratories at the University of Rochester Medical Center, Rochester, NY. MICs of SOLI and comparator drugs were determined for 21 clinical strains of *G. vaginalis* cultured from vaginal specimens collected in 2012.

MIC Determinations. Prior to testing, *G. vaginalis* was subcultured onto Columbia Agar supplemented with 5% sheep blood, colistin and nalidixic acid for 48 hours at 36ºC in ambient air supplemented with 5% CO_2. MICs of SOLI and comparator drugs for *G. vaginalis* were determined by broth microdilution methodology in cation-adjusted Mueller-Hinton broth supplemented with 2.5% lysed horse blood as recommended by CLSI M7-A8 (7). Organism suspensions harvested from fresh agar cultures were adjusted to yield a final test inoculum of 5 x 10^5 CFU/ml. Inoculated microdilution trays were incubated for 72 hours at 36ºC in ambient air supplemented with 5% CO_2. The MIC endpoints for drugs were read as the concentrations at which no growth or a significant reduction of growth was observed by visual inspection after incubation.

The performance of test reagents (including drug potency), equipment, and test personnel were monitored using anaerobic quality control organisms as recommended by CLSI M100-S22 (8). Monitoring of drug potency using aerobic quality control organisms as recommended by CLSI was performed for those drugs lacking CLSI-approved anaerobic quality control ranges. MICs of all drugs for quality control organisms tested in parallel with test organisms were within acceptable ranges as recommended by CLSI.

Results

MICs of SOLI and comparator drugs for 21 clinical strains of *G. vaginalis* were determined. The range of MICs, MICs for 50% of strains and MICs for 90% of strains for all drugs are presented in Table 1. The frequency MIC distributions of each drug for all strains tested are presented in Table 2.

Results (continued)

Table 1: MICs of Solithromycin and Comparator Drugs against *G. vaginalis* (N=21)

Drugs	MIC (µg/ml)		
	MIC Range	MIC 50%	MIC 90%
Solithromycin	≤0.002 - 0.12	0.015	0.12
Penicillin	≤0.03 - 0.25	0.06	0.25
Cefixime	0.25 - 32	2	32
Ceftriaxone	0.06 - 1	0.12	0.5
Azithromycin	≤0.015 - 32	0.06	8
Clarithromycin	≤0.015 - 0.5	≤0.015	0.25
Clindamycin	≤0.03 - 0.25	≤0.03	0.12
Doxycycline	0.03 - 8	0.25	2
Metronidazole	16 - >64	64	64

Table 2: Distribution MICs of Solithromycin and Comparator Drugs against *G. vaginalis* (N=21)

Drugs	MIC (µg/ml)															
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64
Solithromycin	2		3	11	2		3										
Penicillin					9	7	2	3									
Cefixime								2		4	5	5	1	1	3		
Ceftriaxone						5	7	4	4	1							
Azithromycin				4	3	6	2						5		1		
Clarithromycin				12	2	1	1	3	2								
Clindamycin					14	4	1	2									
Doxycycline					1	2	4	10	1		1	1	1				
Metronidazole														3	5	12	1

Conclusions

The MIC of SOLI for 100% of the 21 clinical strains of *G. vaginalis* tested was ≤0.12 µg/ml. SOLI was more active than metronidazole and comparable to clindamycin against *G. vaginalis*. Relative to the older macrolide azithromycin, which is also used in urethritis and gonorrhea, SOLI is about 4-fold more potent. Additionally, gonococci are increasingly resistant to azithromycin, which is no longer recommended to be used in monotherapy for gonorrhea (9).

SOLI is being tested in a global Phase 3 study in uncomplicated bacterial urethritis. SOLI is potent in vitro against *G. vaginalis* and could potentially be useful in cases of *G. vaginalis* mono-infection or mixed infections with gonococcus and chlamydia.

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