

Abstract

Amended Abstract

Background: Cethromycin (CTY) is a novel ketolide that exhibits potent activity against bacterial respiratory pathogens, and is completing Phase 3 clinical trials for the treatment of community acquired pneumonia (CAP). To support CTY's clinical development this surveillance initiative was performed to establish a baseline of CTY activity against a broad collection of contemporary US SP isolates.

Methods: During 2005-2007, SP (n = 2,499) isolates collected from laboratories distributed across each of the nine US Bureau of Census regions were centrally tested by both microdilution according to CLSI methodology (M7-A7; M100- S17). Isolates were tested against CTY, telithromycin (TEL), and other relevant comparators and analysis was stratified according to penicillin (PEN) and erythromycin (ERY) susceptibility and multi-drug resistant (MDR) status. MDR was defined as concurrent resistance to ≥2 of the following agents: PEN, ERY, trimethoprim-sulfamethoxazole (SXT), and cefuroxime (CFX).

Results:

Category (N)	CTY				TEL			
	Range	MIC ₅₀	MIC ₉₀	MIC ₉₅	Range	MIC ₅₀	MIC ₉₀	MIC ₉₅
	0.004	0.004	0.006	0.008	0.008	0.008	0.008	0.012
All (2,499)	<0.0005-1	0.004	0.004	0.006	<0.002-4	0.008	0.008	0.015
PEN S (1,273)	<0.0005-1	0.004	0.004	0.03	<0.002-1	0.008	0.008	0.12
PEN NS (1,226)	<0.0005-0.5	0.004	0.008	0.06	<0.002-4	0.008	0.008	0.5
ERY S (1,724)	<0.0005-0.03	0.004	0.004	0.008	<0.002-0.06	0.008	0.008	0.008
ERY NS (775)	<0.0005-1	0.015	0.03	0.12	0.004-4	0.5	0.25	0.5
MDR (584)	<0.0005-0.5	0.004	0.03	0.12	0.004-4	0.5	0.12	0.5
Non-MDR (1,915)	<0.0005-1	0.004	0.004	0.015	<0.002-4	0.008	0.008	0.06

S=susceptible; NS=non-susceptible

Conclusions: CTY demonstrated potent *in vitro* activity against all SP populations studied, regardless of their resistance phenotype. Based on MIC₅₀s, overall CTY was more active than TEL. These findings demonstrate that CTY has the potential to be a potent therapeutic option for the treatment of CAP, even for infections caused by strains resistant to currently available agents.

Background

The activity of ketolides, semi-synthetic derivatives of erythromycin, is of interest due to their relative stability against known mechanisms of macrolide resistance (methylation and efflux). Ketolides are particularly attractive agents for the treatment of respiratory tract infections, due to the widespread resistance to beta-lactams and macrolides encountered among *S. pneumoniae*, a common respiratory tract pathogen. Cethromycin is a novel ketolide that exhibits potent *in vitro* activity against penicillin and macrolide non-susceptible *S. pneumoniae*. This agent is in the late-stages of development, completing Phase III clinical trials for the treatment of community acquired pneumonia (CAP). Its potential for the treatment of CAP is of particular significance as CAP represents the sixth most common cause of death in the United States¹. To support the clinical development of cethromycin, this surveillance initiative was performed to establish a baseline of cethromycin activity against a broad collection of contemporary *S. pneumoniae* isolates from the US.

Methods

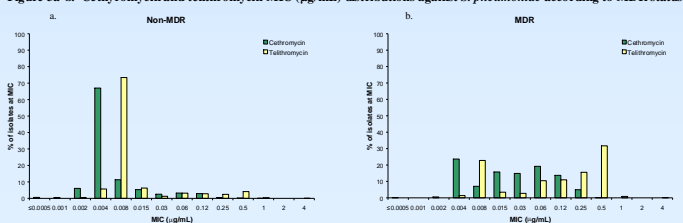
During 2005-2007, a total of 2,499 *S. pneumoniae* isolates were collected from 187 hospital laboratories distributed across each of the nine US Bureau of Census regions and were centrally tested by both microdilution according to CLSI methodology (M7-A7; M100- S17). Isolates were tested against cethromycin, telithromycin and other relevant comparators such as erythromycin, azithromycin, clarithromycin, and penicillin. Analysis was stratified according to penicillin and erythromycin susceptibility and multi-drug resistant (MDR) status. MDR was defined as concurrent resistance to ≥2 of the following agents: penicillin, erythromycin, trimethoprim-sulfamethoxazole (SXT), and cefuroxime.

Table 1. MIC (µg/mL) activity of cethromycin and comparators against *S. pneumoniae*

Phenotype ^a	Agent	Total n	MIC (µg/mL)				nS (%)	nI (%)	nR (%)	nR (%)
			Range	MIC ₅₀	MIC ₉₀	MIC ₉₅				
All	Cethromycin	2,499	<0.0005-1	0.004	0.004	0.06	>	>	>	
	Telithromycin		<0.002-4	0.008	0.008	0.5	2,497 (99.9)	0	2 (0.1)	
	Erythromycin		<0.015-4	0.03	0.06	>4	1,724 (69.0)	3	772 (30.9)	
	Azithromycin		<0.015-4	0.06	0.12	>4	1,727 (69.1)	2	770 (30.8)	
	Clarithromycin		<0.015-4	0.03	0.03	>4	1,727 (69.1)	8	764 (30.6)	
PEN S	Cethromycin	1,273	<0.0005-1	0.004	0.004	0.03	>	>	>	
	Telithromycin		<0.002-1	0.008	0.008	0.12	1,273 (100)	0	0 (0)	
	Erythromycin		<0.015-4	0.03	0.03	>4	1,073 (84.3)	1	199 (15.6)	
	Azithromycin		<0.015-4	0.06	0.06	>4	1,074 (84.4)	0	199 (15.6)	
	Clarithromycin		<0.015-4	0.03	0.03	>4	1,074 (84.4)	5	194 (15.2)	
PEN NS	Cethromycin	1,226	<0.0005-0.5	0.004	0.004	0.06	>	>	>	
	Telithromycin		<0.002-4	0.008	0.008	0.5	1,224 (99.8)	0	2 (0.2)	
	Erythromycin		<0.015-4	>4	0.06	>4	651 (53.1)	2	573 (46.7)	
	Azithromycin		<0.015-4	>4	0.12	>4	653 (53.3)	2	571 (46.6)	
	Clarithromycin		<0.015-4	0.03	0.03	>4	653 (53.3)	3	570 (46.5)	
ERY S	Cethromycin	1,724	<0.0005-0.03	0.004	0.004	0.008	>	>	>	
	Telithromycin		<0.002-0.06	0.008	0.008	0.008	1,724 (100)	0	0 (0)	
	Erythromycin		<0.015-0.25	0.03	0.03	0.06	1,724 (100)	0	0 (0)	
	Azithromycin		<0.015-0.5	0.06	0.06	0.12	1,724 (100)	0	0 (0)	
	Clarithromycin		<0.015-0.25	0.03	0.03	0.06	1,724 (100)	0	0 (0)	
ERY NS	Cethromycin	775	<0.0005-1	0.015	0.03	0.12	>	>	>	
	Telithromycin		0.004-4	0.5	0.25	0.5	773 (99.7)	0	2 (0.3)	
	Erythromycin		0.5-4	>4	>4	>4	0	0	772 (99.6)	
	Azithromycin		0.5-4	>4	>4	>4	0	0	770 (99.5)	
	Clarithromycin		0.06-4	>4	>4	>4	3	0	764 (98.6)	
MDR ^b	Cethromycin	584	<0.0005-0.5	0.004	0.03	0.12	>	>	>	
	Telithromycin		0.004-4	0.5	0.12	0.5	583 (99.8)	0	1 (0.2)	
	Erythromycin		<0.015-4	>4	>4	>4	146 (25.0)	0	438 (75.0)	
	Azithromycin		<0.015-4	>4	>4	>4	146 (25.0)	0	437 (74.8)	
Non-MDR	Cethromycin	1,915	<0.0005-1	0.004	0.004	0.015	>	>	>	
	Telithromycin		<0.002-4	0.008	0.008	0.06	1,914 (99.9)	0	1 (0.1)	
	Erythromycin		<0.015-4	0.03	0.03	>4	1,578 (82.4)	3	334 (17.4)	
	Azithromycin		<0.015-4	0.06	0.06	>4	1,581 (82.6)	1	333 (17.4)	
	Clarithromycin		<0.015-4	0.03	0.03	>4	1,581 (82.6)	5	329 (17.2)	
	Clarithromycin		<0.015-4	>4	>4	>4	146 (25.0)	3	435 (74.5)	

^aPEN, penicillin; ERY, erythromycin; MDR, multi-drug resistant; S, susceptible; NS, non-susceptible
^bCLSI breakpoints for susceptible (S), intermediate (I), and/or resistant (R) interpretation not available
^cMDR defined as concurrent resistance to ≥2 of the following agents: penicillin, erythromycin, trimethoprim-sulfamethoxazole, and cefuroxime

Figure 3a-b. Cethromycin and telithromycin MIC (µg/mL) distributions against *S. pneumoniae* according to MDR status



Results

Figure 1a-b. Cethromycin and telithromycin MIC (µg/mL) distributions against *S. pneumoniae* according to penicillin susceptibility

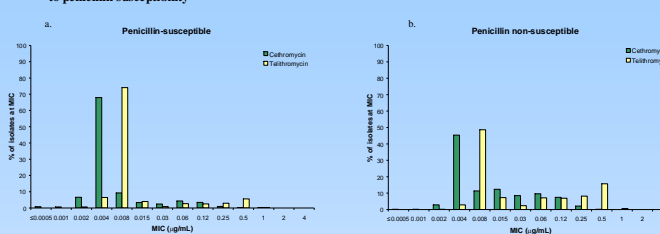
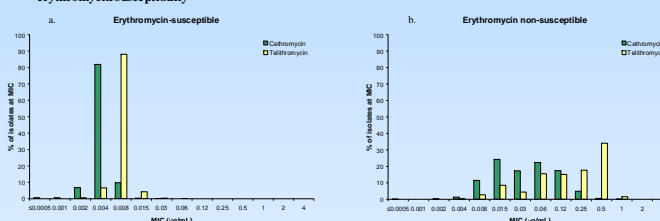


Figure 2a-b. Cethromycin and telithromycin MIC (µg/mL) distributions against *S. pneumoniae* according to erythromycin susceptibility



Based on MIC₅₀ (µg/mL), cethromycin was more active than telithromycin against *S. pneumoniae* overall by three-doubling dilutions (0.06 µg/mL versus 0.5 µg/mL, respectively) and was at least six-doubling dilutions more active compared to other macrolide agents (>4 µg/mL) (Table 1).

The activity of cethromycin against penicillin-susceptible isolates (MIC₅₀ = 0.004 µg/mL, MIC₉₀ = 0.03 µg/mL) was not notably altered against penicillin non-susceptible isolates (MIC₅₀ = 0.008 µg/mL, MIC₉₀ = 0.06 µg/mL) (Table 1). It was more active than telithromycin by both MIC₅₀ and MIC distribution regardless of penicillin status (Figure 1a-b).

The activity of cethromycin was lower against erythromycin non-susceptible isolates (MIC₅₀ = 0.03 µg/mL, MIC₉₀ = 0.12 µg/mL) relative to erythromycin-susceptible isolates (MIC₅₀ = 0.004 µg/mL, MIC₉₀ = 0.008 µg/mL) (Table 1, Figure 2a-b). Cethromycin was more active than telithromycin by both MIC₅₀ (Table 1) and MIC distribution regardless of erythromycin status (Figure 2a-b).

Among the tested isolates, 30.9% were resistant to erythromycin, 14.7% were resistant to penicillin, 22.8% were resistant to SXT, and 20.5% were resistant to cefuroxime. Against MDR *S. pneumoniae* (resistant to ≥2 of the above agents), the activity of cethromycin was superior to that of telithromycin with MIC₅₀s of 0.12 µg/mL and 0.5 µg/mL, respectively (Table 1) and MIC ranges of <0.0005-0.5 µg/mL for cethromycin versus 0.004-4 µg/mL for telithromycin (Table 1, Figure 3b).

Conclusions

Against all *S. pneumoniae* populations, cethromycin demonstrated potent *in vitro* activity, regardless of their resistance phenotype. Cethromycin activity was not affected by penicillin resistance, but cethromycin MICs were increased among MDR and erythromycin resistant populations.

Cethromycin was more active than telithromycin, a comparator ketolide, and had superior *in vitro* activity against resistant *S. pneumoniae* relative to tested macrolides by MIC₅₀ and MIC₉₀.

These findings support the cethromycin program and further reveal the potential of cethromycin to be a potent therapeutic option for the treatment of CAP and other respiratory tract infections, including those caused by *S. pneumoniae* strains resistant to penicillin and macrolides.

References

1. T. File. *Streptococcus pneumoniae* and community-acquired pneumonia: A cause for concern. American Journal of Medicine Supplement 117(3): 39-50, 2004.

Acknowledgement

This study was supported by Advanced Life Sciences, Woodridge, Illinois