Comparative In Vitro Susceptibilities of a New Investigational Macrolide CEM-101 Against Human Mycoplasmas & Ureaplasmas

Abstract

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Background: CEM-101 (Cempra Pharmaceuticals, Inc.) is a promising new macrolide in development for treating community acquired macrolide-resistant bacteria as well as macrolide-susceptible bacteria. We performed an in vitro study to determine the activity of CEM-101 in comparison to azithromycin (AZI), telithromycin (TEL), doxycycline (DOX), levofloxacin (LEV), clindamycin (CL), and linezolid (LZD) against clinical isolates of 6 human mycoplasma and ureaplasma species. Organisms tested included 38 Mycoplasma pneumoniae (MP), 5 Mycoplasma genitalium (MG), 13 Mycoplasma hominis (MH), 15 Mycoplasma fermentans (MF), 10 Ureaplasma parvum (UP) and 10 Ureaplasma urealyticum (UU). Methods: Microbroth dilution was used to determine MICs using 100 broth for ureaplasmas and 1% broth for mycoplasma species. MICs were determined for 9 isolate pairs. Results: MICs for CEM-101 ranged from 0.00000500 – 0.5 µg/ml with MIC90 = 0.000125 µg/ml, making its activity 4-fold > AZI, 8-fold > TEL. LZD was the least active tested against MP with MIC90 = 128 µg/ml. Two macrolide-resistant MP with AZI and TEL MICs ≥ 32 µg/ml were inhibited by CEM-101 at 0.5 µg/ml. MICs for all 4 isolates were > 16-fold greater than MICs for 9 MP indicating the drug is bactericidal. All mycoplasma and ureaplasma isolates were inhibited by CEM-101 at concentrations ≤ 0.5 µg/ml, making it the most potent compound tested overall. Excluding 2 macrolide-resistant MP, no isolate of any species tested had an MIC > 0.008 µg/ml for CEM-101. Conclusions: CEM-101 showed excellent activity in vitro against human mycoplasmas and ureaplasmas, including macrolide-resistant MP, doxycycline-resistant UP and UU and was more potent than comparator drugs.

Introduction

Mycoplasma pneumoniae, M. hominis, M. genitalium, and M. fermentans can be responsible for infections in the respiratory and urogenital tracts. Macrolides have historically been the treatment of choice for M. pneumoniae respiratory infections of adults and children because they have the advantages of being safe and well tolerated in oral formulations, possess anti-inflammatory properties independent of their antibacterial activities, and activity against other microorganisms that may cause clinically similar illness. These properties have been questioned by recent reports of increased macrolide resistance in M. pneumoniae and other mycoplasmas. Studies have not been confirmed by microbial testing. Macrolides are also active against other Mycoplasma spp. as well as Ureaplasma spp. M. fermentans and M. hominis which are generally resistant to several members of this class, but are chlamydiae-susceptible [1]. During the past several years, concerns have arisen over the impact of widespread use of macrolides on antimicrobial resistance in respiratory pathogens such as Streptococcus pneumoniae such that 30% to 50% of clinical isolates are no longer susceptible to macrolides due mainly to efflux and/or bacterial methylation [2] and may not respond to treatment with these drugs [3]. The belief that macrolide resistance can develop naturally in M. pneumoniae is plausible since it is only a single-stranded genome and in vivo selection of resistant mutants is more likely to occur in these organisms. Several studies have reported that 32% of M. pneumoniae isolates that may have clinical implications on patient outcome [4,5]. These studies have also reported that 10-20% of M. fermentans are macrolide-resistant [6]. The US Centers for Disease Control and Prevention described 3 of 11 cases (27%) of M. pneumoniae infections from a recent outbreak that were macrolide-resistant and had a 23S rRNA mutation [7]. These findings clearly indicate the need for new drug classes or improvements in drugs of existing classes such as the macrolides.

C1EM-101 is a new macrolide active against many bacteria that cause respiratory and/or genital infections, such as M. pneumoniae, M. hominis, M. genitalium, M. fermentans, Ureaplasma spp., Chlamydia spp., Neisseria spp., Streptococcus pneumoniae, and Haemophilus influenzae. However, a recent study by Cempra Pharmaceuticals, Inc. demonstrated that CEM-101 was bactericidal against 16S rRNA of 25 species of S. pneumoniae and M. pneumoniae with MICs of ≤ 0.5 µg/ml. This study confirmed the excellent antimicrobial spectrum of CEM-101, we studied in vitro activities against human mycoplasmas and ureaplasmas.

Methods

Microorganisms

All M. pneumoniae were cultured from the respiratory tract of adults and children with pneumonia between 1992 and 2006, 2 isolates collected from children in Birmingham, Al, in 2005 were macrolide-resistant (azithromycin MICs > 32 µg/ml). 5 M. genitalium isolates (MG), 13 Mycoplasma hominis (MH), 15 M. fermentans (MF), 10 Ureaplasma parvum (UP) and 10 Ureaplasma urealyticum (UU) were tested. MICs were determined for 9 isolate pairs. Methods: Microbroth dilution was used to determine MICs using 100 broth for ureaplasmas and 1% broth for mycoplasma species. MICs were determined for 9 isolate pairs. Results: MICs for CEM-101 ranged from 0.00000500 – 0.5 µg/ml with MIC90 = 0.000125 µg/ml, making its activity 4-fold > AZI, 8-fold > TEL. LZD was the least active tested against MP with MIC90 = 128 µg/ml. Two macrolide-resistant MP with AZI and TEL MICs ≥ 32 µg/ml were inhibited by CEM-101 at 0.5 µg/ml. MICs for all 4 isolates were > 16-fold greater than MICs for 9 MP indicating the drug is bactericidal. All mycoplasma and ureaplasma isolates were inhibited by CEM-101 at concentrations ≤ 0.5 µg/ml, making it the most potent compound tested overall. Excluding 2 macrolide-resistant MP, no isolate of any species tested had an MIC > 0.008 µg/ml for CEM-101. Conclusions: CEM-101 showed excellent activity in vitro against human mycoplasmas and ureaplasmas, including macrolide-resistant MP, doxycycline-resistant UP and UU and was more potent than comparator drugs.

MIC Testing

Antibiotic powders were dissolved as instructed by the manufacturer and frozen in 1 ml aliquots containing 250 µg/ml. Drugs were included (CEM-101, azithromycin, telithromycin, doxycycline, levofloxacin, and clindamycin) and no dilution. A working solution of each drug was prepared on the day of testing based on the anticipated MIC ranges for each drug. Serial 2-fold antibiotic dilutions were performed in 10B broth for Ureaplasma spp. and 24 broth for Mycoplasma spp. in well mixing plates as previously described [8]. For macrolides and tetracyclines tested against M. pneumoniae, dilutions were taken down to 0.00000500 µg/ml to measure the endpoint MIC for these potent agents.

MIC Summary

Results

M. pneumoniae Macrolide MIC Distribution

Tables and Figures

Conclusions

All mycoplasma and ureaplasma isolates were inhibited by CEM-101 at concentrations ≤ 0.5 µg/ml, making it the most potent compound tested overall. M. pneumoniae MICs for CEM-101 ranged from 0.00000500 – 0.5 µg/ml with MIC90 = 0.000125 µg/ml, making its activity 4-fold > AZI, 8-fold > TEL. LZD was inactive against M. pneumoniae, but some M. fermentans and M. hominis had MICs ≤ 1 mg/ml. 2 macrolide-resistant MP (ren-AZI and TEL MICs ≥ 32 µg/ml) were inhibited by CEM-101 at 0.5 µg/ml. CEM-101 MICs were ≤ 16-fold greater than MICs for M. pneumoniae indicating the drug is bactericidal against this organism.

CEM-101 was active against all 10 clinical isolates of M. hominis and Ureaplasma spp.

Excluding 2 macrolide-resistant MP, no isolate of any species tested had an MIC > 0.008 µg/ml for CEM-101.

References