In vitro and In vivo activity of CEM-101, a new fluoroketolide, against Mycobacterium avium complex

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Background:

M. avium complex (MAC) infection is a serious health concern for AIDS patients. Standard treatment regimens consist of clarithromycin (CLA), ethambutol and a rifamycin. Treatment failure is often attributed to the emergence of CLA-resistance. A new fluoroketolide, CEM-101, has demonstrated potent activity against several gram positive bacteria. This study was undertaken to compare the in vitro activity of CEM-101 to CLA against both CLA-susceptible (S) and resistant (R) isolates of MAC as well as comparing the in vivo activity against a CLA-S isolate.

Methods:

In vitro: The MICs of CLA and CEM-101 were measured against 24 MAC isolates using a microtiter broth dilution assay. There were 12 CLA-S and 12 CLA-R isolates evaluated. In vivo: Forty-two six-week old female C57BL/6 mice were infected intranasally with 2.4 X 10⁷ CFU of MAC ATCC 49601. Treatment with CLA at 200mg/kg or CEM-101 at 200, 100, 50 or 25mg/kg was started one week post-infection and administered by gavage 5 days per week for 4 weeks. Early and late control groups were utilized to determine the infection load at the initiation and completion of therapy, respectively. Mice were euthanized at the completion of therapy and their spleens and right lungs were processed to determine their infection load.

Results:

The MICs of CLA against the CLA-S strains ranged from 0.125 to 8mg/ml while the MICs for CEM-101 ranged from 0.125 to 16mg/ml. The MICs of CLA against the CLA-R isolates ranged from 32 to 128mg/ml while the range for CEM-101 was 8 to 16mg/ml. In vivo CEM-101 at 200mg/kg was better than CLA at 200mg/kg in both the spleens and lungs. CEM-101 activity was dose dependent.

Conclusions:

CEM-101 had potent activity against both CLA-S and CLA-R MAC and demonstrated better activity compared to CLA in the mouse model of MAC infection. Considering the excellent tissue and intracellular distribution, and low metabolism of CEM-101 in man, CEM-101 may have the potential of replacing CLA in treatment regimens against CLA-resistant MAC infection.