A Novel Macrolide/Fluoroketolide, Solithromycin Exerts Superior Anti-inflammatory Effect via NF-κB Inhibition in COPD Cells

Abstract 1613

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Background:

Macrolides are reported to reduce exacerbation of chronic obstructive pulmonary disease (COPD) and also show anti-inflammatory effects in vitro and in vivo. However the anti-inflammatory efficacies of current macrolides are not optimal. In this study, we evaluated the anti-inflammatory effects of solithromycin (CEM-101), a novel macrolide/fluoroketolide, and those of other macrolides commercially available.

Methods:

Effects of solithromycin on LPS-induced TNFα and/or CXCL8 release, PMA-induced MMP9 activity and NF-κB activity under oxidative stress have been evaluated and compared with the effects of erythromycin, clarithromycin and azithromycin in human monocytic U937 cells and PBMCs obtained from COPD patients. TNFα and CXCL8 were measured by ELISA. MMP9 levels were determined by zymography and NF-κB activity was evaluated by NF-kB-DNA binding assay. We also examined effect of solithromycin on airway neutrophilia in mice exposed to cigarette smoke for 12 days.

Results:

Solithromycin inhibited LPS-induced TNFα/CXCL8 production and MMP9 activity in U937 cells with IC₅₀ values of 78, 42 and 15 µM, respectively, which were more potent than any other macrolide. In addition, solithromycin suppressed TNFα release and MMP9 activity in PBMCs from COPD patients at 10uM, which is 100 times more potent than other macrolides. Activated NF-κB due to oxidative stress (H₂O₂, 200 µM) was completely reversed by solithromycin. Solithromycin (100mg/kg,po) also inhibited cigarette smoke-induced neutrophilia, which is corticosteroid insensitive.

Conclusions:

Solithromycin showed better anti-inflammatory profiles compared with macrolides currently used in clinic, and could be a promising anti-inflammatory and anti-microbial macrolide/fluoroketolide for the treatment of COPD.