

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

Abstract 1613

Yoshiki Kobayashi¹, Hiroo Wada², Peter J. Barnes¹, Prabha Fernandes³ and Kazuhiro Ito¹

¹Airway Disease Section, National Heart and Lung Institute, Imperial College London, London, United Kingdom, ²Cempra, Inc., Chapel Hill, North Carolina

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 TNF α and/or CXCL8 release, PMA-induced MMP9 activity and NF- κ B 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. TNF α and CXCL8 were measured by ELISA. MMP9 levels were determined by zymography and NF- κ B activity was evaluated by NF- κ B-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 TNF α /CXCL8 production and MMP9 activity in U937 cells with IC₅₀ values of 78, 42 and 15 μ M, respectively, which were more potent than any other macrolide. In addition, solithromycin suppressed TNF α release and MMP9 activity in PBMCs from COPD patients at 10 μ M, which is 100 times more potent than other macrolides. Activated NF- κ B due to oxidative stress (H₂O₂, 200 μ M) 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.