Title: Macrolides inhibit cytokine production by alveolar macrophages in bronchiolitis obliterans organizing pneumonia

Dr. Miaotian 1757 Cai cici0511@sina.com MD 1,2, Dr. Francesco 1758 Bonella Francesco.Bonella@ruhrlandklinik.uk-essen.de MD 1, Prof. Dr Huaping 1759 Dai daihuaping@sina.com MD 1,2, Prof. Dr Rafael 1760 Sarria rafael.sarria@ehu.es MD 3, Prof. Dr Josune 1761 Guzman josune.guzman@ruhruni-bochum.de MD 4 and Prof. Dr Ulrich 1762 Costabel ulrich.costabel@ruhrlandklinik.uk-essen.de MD 1. 1 Department of Pneumology and Allergology, Ruhrlandklinik, University Hospital, Essen, Germany, 45239 ; 2 Beijing Institute of Respiratory Medicine, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China ; 3 Department of Neurosciences, Faculty of Medicine and Dentistry, Basque Country University, Bilbao, Spain and 4 General and Experimental Pathology, Ruhr University, Bochum, Germany.

Body: Background and objective: Bronchiolitis obliterans organizing pneumonia (BOOP) is a distinct clinicopathological entity histologically characterized by intra-alveolar granulation tissue and absence of extensive fibrotic lesions. Effective macrolide treatment of BOOP has been reported anecdotally. This study aimed to investigate whether alveolar macrophages (AMs) produce aberrant proinflammatory cytokines in BOOP and whether this can be inhibited by clarithromycin (CAM) or azithromycin (AZM). Methods: AMs collected by bronchoalveolar lavage (BAL) from 6 BOOP patients and 8 non-ILD controls were cultured for 24 hours in the presence or absence of CAM, AZM, lipopolysaccharide (LPS), or dexamethasone (DEX). Tumor necrosis factor alpha (TNF-α), soluble TNF receptor 1 (sTNFR1), sTNFR2, interleukin 1beta (IL-1β), IL-6, IL-8, IL-10, interferon gamma inducible protein 10 (IP-10) and CC chemokine ligand 18 (CCL18) were measured in the culture supernatant by ELISA. Results: The spontaneous and LPS-stimulated production of all investigated cytokines by AMs was significantly increased in BOOP compared to controls. CAM and AZM induced a dose-dependent suppression of spontaneous TNF-α, sTNFR2, IL-6, IL-8 and CCL18 production (p < 0.05). CAM also inhibited the IL-1β production. CAM and AZM significantly and dose-dependently attenuated the LPS-stimulated production of sTNFR1, sTNFR2, IL-8 and CCL18 (p < 0.05). CAM also inhibited the LPS-stimulated TNF-α, IL-1β, IL-6 and IL-10 production. Conclusions: AMs from BOOP patients produce abundant proinflammatory cytokines which may be pivotal in the disease pathogenesis. Macrolides inhibit this cytokine production, CAM more efficiently than AZM.