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Title: Synergistic effects of p38 MAPK inhibition with a corticosteroid in alveolar macrophages from corticosteroid insensitive asthma patients

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Body: Background: Some asthma patients remain symptomatic despite using inhaled corticosteroids (CS) and long-acting- β_2 -agonists. P38 MAPK inhibitors are novel anti-inflammatory drugs that may be useful in CS insensitive asthma patients. We used alveolar macrophages (AM) to investigate the effects of p38 MAPK inhibition in CS insensitive asthma patients. Methods: AM from 27 asthma patients (6 GINA1, 10 GINA2 and 11 GINA3/4) were stimulated with LPS (1 μ g/ml). The effects of dexamethasone (dex: 1-1000nM), the p38 MAPK inhibitor BIRB-796 (1-1000nM) and both drugs combined at all concentrations on supernatant TNF α , IL-6 and IL-8 levels were analysed by ELISA. Dose-sparing and efficacy enhancing effects of combination treatment were determined as per Armstrong et al. J Pharmacol Exp Ther 2011; 338:732-40. Results: Dex reduced LPS-induced TNF α , IL-6 and IL-8 in all groups, but the maximum inhibition was significantly reduced for GINA3/4 compared to GINA2 and GINA1 (p<0.01). A subgroup of CS 'insensitive' patients (n=7; 6 GINA3/4 and 1 GINA2) were identified by the in vitro AM response to dex. BIRB-796 in combination with dex significantly increased cytokine inhibition compared to dex alone (p<0.001) in all groups. This effect was greater in 'insensitive' compared to 'sensitive' patients with efficacy enhancing benefits of 36.4 and 10.8 respectively for inhibition of LPS-induced TNF α . Conclusion: A high proportion of GINA3/4 patients have CS 'insensitive' AM. P38 MAPK inhibitors enhance the efficacy of CS; This effect is greater in the 'insensitive' population, suggesting that identifying subsets of patients may be key to developing novel therapeutics.