The effect of a selective CRTh2 antagonist on tobacco smoke (TS) induced airway inflammation and remodelling in the mouse


Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) was initially identified as an orphan GPCR highly expressed on human Th2 cells, eosinophils and basophils. It was de-orphanised in 2001 when PGD2 was shown to be an endogenous agonist, a finding that has prompted a re-evaluation of the role of PGD2 in allergic diseases such as rhinitis and asthma. AstraZeneca (AZ) have highlighted CRTh2 is also expressed on lung epithelial cells. This encouraged AZ to assess the effects of a selective CRTh2 antagonist (AZ11805131; (2-[2-(4-ethylsulfonyl-2-methyl-phenyl)-4-(trifluoromethyl)phen- oxy]acetic acid), in the Argenta murine 11 day TS model, which has a remodelling profile of active epithelial degeneration and proliferative repair and lymphoid reactions (Fox et al., 2007).

Female C57/Bl6/J mice were orally dosed with vehicle (0.5% hydroxypropylmethyl cellulose (HPMC, w/v)/ 0.1% Tween 80 (v/v) in water), AZ11805131 (0.15, 0.5 or 1.5 mg/kg b.i.d.) or Roflumilast (5 mg/kg u.i.d.); n=10 per group. 24 hrs after the last TS exposure, mice were anaesthetised (pentobarbitone Na, 100 mg/kg i.p.) and blood samples taken for plasma measurements of AZ11805131. Bronchoalveolar lavage (BAL) was performed, cells recovered and total and differential cell counts made; supernatants were frozen for measurement of inflammatory mediators (IM). The lungs were insufflated with 10% buffered formalin and removed for histological evaluation. IM in BAL were measured using a Luminex multiplex assay (Bafadhel et al, 2009). Statistical significance of p ≤ 0.05 for BAL cell counts was tested using one-way analysis of variance test (ANOVA), followed by a Bonferroni correction and IM were tested using a Dunns test. TS exposure resulted in a significant increase in BAL leucocytes, lung pathology and IM (KC, GMCSF, MCP-1, TNFα, IL-1α, GCSF, IL-6 and IP10). Roflumilast, significantly inhibited BAL leucocytes and lung pathology. Treatment with AZ1180531 resulted in a dose-dependent statistically significant inhibition of total leucocytes, neutrophils, macrophages, eosinophils, lymphocytes and epithelial cells in BAL. AZ11805131 exposures were equivalent to Cmin concentrations of 3, 10 and 30 times pIC50 for CRTh2 inhibition. AZ11805131 did not inhibit any IM in BAL. Lung pathology confirmed a reduction in leucocyte infiltration. A marked suppression of TS-related mucosal pathology was seen, even in airways presenting with a prominent leucocyte cuffing. Indeed, some airway zones showed no significant mucosal pathology at all. These observations led to the hypothesis that AZ11805131 exerted a direct 'cytoprotective' effect on the mucosa by a mechanism distinct from that linked with suppression of leucocytic inflammation. To investigate this, the effects of AZ11805131 on an existing inflammatory response were studied. Mice were dosed (1.5 mg/kg b.i.d.) before (prophylactic) or after 5 days (therapeutic) of TS exposure. Prophylactic dosing of AZ11805131 confirmed the previous results and similar effects were seen with therapeutic dosing. This suggests CRTh2 antagonists may be effective in the treatment of COPD.