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Title: Effects of the novel toll-like receptor 7 (TLR7) agonist AZD8848 on allergen-induced responses in patients with mild asthma

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Body: Background: AZD8848 is an antedrug TLR7 agonist being evaluated for treatment of asthma and allergic rhinitis. This double-blind, placebo-controlled, randomised, parallel-group trial (NCT00999466) investigated efficacy, safety and tolerability of intranasal (IN) AZD8848 in mild-to-moderate allergic asthma patients (pts) who were subsequently challenged with an inhaled allergen. Methods: 51 pts (mean age 32 yrs) with a confirmed late asthmatic response (LAR) received 8 once-weekly IN doses of AZD8848 60µg (n=26) or placebo (n=25). Key assessments of efficacy and safety were made at 1 and 4 weeks (wk) after last dose of study drug. Results: Allergen-induced LAR was 27% lower with AZD8848 than placebo at 1 wk after last dose ($p=0.035$); no differences were seen at 4 wk. Similarly, AZD8848 reduced allergen-induced airway methacholine responsiveness at 1 wk ($p<0.05$) but not at 4 wk. There was no significant effect on allergen-induced increases in sputum eosinophils and Th2 cytokines. AZD8848 was safe and generally well tolerated; most AZD8848-related adverse events were mild and consisted of headache and influenza-like symptoms. Plasma AZD8848 concentrations (as metabolite) peaked 15 min after last dose, then rapidly declined to undetectable levels. Conclusions: IN AZD8848 attenuated allergen-induced LAR and allergen-induced increases in airway methacholine responsiveness 1 wk after 8 weekly doses, but these effects were not maintained at 4 wk. AZD8848 was safe and generally well tolerated. The data show that IN administration of a TLR7 agonist can ameliorate allergen-induced responses in the lower airways.
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