

A Potent and Selective CRTh2 Antagonist is Efficacious in a Model of Atopic Dermatitis

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Abstract

Prostaglandin D2 (PGD2) is a potent prostanoid released from activated mast cells during atopic responses. CRTh2 (Chemoattractant Receptorhomologous molecule expressed on Th2 lymphocytes; a.k.a. DP2), a PGD2receptor, mediates chemotaxis and mast cell-dependent activation of basophils, eosinophils and Th2 lymphocytes. Preclinical data and emerging clinical results suggest CRTh2 antagonists may have utility in allergic diseases. ARRY-005 is a potent, selective, orally bioavailable competitive antagonist of CRTh2 (binding IC50 = 1 nM). ARRY-005 inhibits i) PGD2-mediated chemotaxis of isolated human basophils, ii) PGD2-induced eosinophil shape change in human whole blood and iii) PGD2-induced CRTh2 receptor internalization in human whole blood. In a model of atopic dermatitis (AD) utilizing NC/Nga mice that spontaneously develop symptoms of AD, oral administration of ARRY-005 at 30mg/kg (QD) inhibited ear edema, erythema, oozing, crust formation, hemorrhaging and pruritus and showed trends in improved skin histopathology. The selective CRTh2 antagonist, ARRY-005, is a potent inhibitor of basophils and eosinophils in vitro and exhibited significant protective activity in a model of dermatitis.

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