FLX193: A Potent, Selective CCR4 Antagonist for Allergic Disorders

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Abstract

Type 2 helper T cells (Th2) cells have been shown to express CCR4 receptor, and play a critical role in driving the pathogenesis of asthma and atopic dermatitis. FLX193 is a best-in-class, highly-potent and selective small molecule CCR4 antagonist under investigation for the treatment of allergic disorders. FLX193 blocked migration of CCR4+ Th2 cells (human and mouse) towards CCL17 and CCL22 in an in vitro chemotaxis assay. FLX193 is well-tolerated in animals at efficacious doses.

In an Ovalbumin (OVA)-induced asthma model, FLX193 significantly reduced lymphocyte and eosinophil counts in the Bronchoalveolar lavage (BAL) fluid and showed a reduction of the effector Th2-relevant cytokines IL-5 and IL-13. FLX193 treatment also reduced the levels of CCL17 and CCL22 in the BAL fluid, indicating an overall reduction of inflammation. In addition, we used an atopic dermatitis mouse model to demonstrate that treatment with FLX193 decreased CCR4+ T-cell mediated inflammation. Hence FLX193 shows promise in the treatment of atopic dermatitis and asthma.

Introduction

- Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease that causes dry skin, intense pruritus (itching), and a red, raised rash; the disease is categorized into mild, moderate, & severe
- AD affects ~19 Million (19M Diagnosed) people in the US and ~43.7M (~20.9M Diagnosed) in the major global markets. About 60% of patients have moderate to severe disease
- Pre-clinical and clinical data have shown a predominant role of Th2 cells in the skin as well as serum
- Human Th2 cells express CCR4 (70-80%) and migrate towards CCR4 ligands
- Hence, in this study we examine whether migration of Th2 cells into inflamed tissue and the increase disease severity is CCR4 dependent

Dose Dependent Inhibition of CCL22-Induced Migration

A) Chemotaxis Assay (CTX)
B) In vitro differentiated mouse and human Th2 cells

4 FLX193 Reduces Ear Thickness in FITC-Induced Skin Inflammation Model

A) FITC-induced skin inflammation model

5 FLX193 Reduces Ear Thickness in OVA-Induced Skin Inflammation Model

A) OVA-induced skin inflammation model

6 FLX193 Is Efficacious in a Model of Allergic Asthma

A) Allergic airway inflammation model
B) Asthma model lung H&E analysis

7 FLX193 Effectively Reduces the cell count and cytokine levels in the BALF

A) Cell count at 24h post last challenge
B) Cytokine and chemokine level at 24h post last challenge

8 Summary and Conclusion

- FLX193 is a highly potent CCR4 oral antagonist for allergic disorders
- FLX193 prevents migration of CCR4+ Th2 cells towards CCL17 and CCL22 in vitro
- In preclinical mouse models of atopic dermatitis and asthma, FLX193 demonstrated anti-inflammatory efficacy comparable to an anti-IL-13 antibody
- Our studies suggest a potential role for FLX193 in treatment of patients with allergic disorders and other inflammatory diseases
- As an orally bioavailable small molecule inhibitor, FLX193 presents a potentially attractive alternative to treatment with injectable biologics or topical corticosteroids

References