KTN0158, a Humanized Anti-KIT Monoclonal Antibody, Reduces Airway Eosinophilia in a Feline Model of Allergic Asthma

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Introduction

• KTN0158 is a humanized immunoglobulin G1 kappa (IgG1) monoclonal antibody (mAb) that specifically binds the membrane-proximal D4 domain of KIT (a mast cell factor growth factor; CD117) and inhibits homotypic interactions of the receptor.
• KIT, a receptor tyrosine kinase, and its ligand, stem cell factor (SCF), have multiple effects on mast-cells and eosinophils in the lung (Oliveira et al., 2003; Reber et al., 2006).
• Mast cells are predominantly regulated by KIT and the high affinity Fc epsilon receptor 1 binding IgE (Oliveira et al., 2003); and have been implicated in a variety of allergic and inflammatory diseases such as asthma (Metcalfe et al., 1997).
• In humans, serum SCF and soluble KIT concentrations correlate with increased mast cell mediator release (Makowska et al., 2009) and the mRNA levels of SCF and KIT are increased in asthmatic patients compared to healthy controls (Al-Muhsen et al., 2004).

Mast Cells and Eosinophils are Key Mediators of Allergic Asthma/Rhinitis

• Mast cells play a significant role in early and late phase responses in allergic asthma and eosinophilic airway eosinophilia.
• Mast cells are predominantly regulated by KIT and the high affinity Fc epsilon receptor 1 binding IgE (Oliveira et al., 2003).
• Inhibition of KIT Signaling by KTN0158

Results

• KTN0158 binds KIT D4-D5 domains from various species and inactivated KIT.
• KTN0158 is a potent inhibitor of SCF-mediated β2-hexosaminidase release caused by mast cell degranulation (IC50=114 μM).
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References


Norris Reinero et al, 2004


Conclusions

• KTN0158 is a potent inhibitor of SCF-induced KIT signaling.
• KTN0158 modulates SCF-mediated effects on degranulation and cytokine release in the LAD2 mast cell line.
• KTN0158 treatment decreased airway eosinophil numbers in both acute and chronic phases of a feline allergic asthma model.
• Collectively, these data suggest that KTN0158 can modulate mast cell and eosinophil function via KIT and warrant further evaluation of KTN0158 as a treatment in mast cell-related diseases such as asthma.
• Studies to investigate the potential benefit of KTN0158 in mast cell-related diseases and inflammation, and to evaluate safety are planned.