Novel Anti-Siglec-8 Antibody Reduces Eosinophil and Mast Cell Infiltration In a Mouse Model of Eosinophilic Gastritis and Gastroenteritis
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BACKGROUND
- Pathologic accumulation and over-activation of mast cells and eosinophils are implicated in multiple chronic inflammatory diseases in the GI tract including eosinophilic esophagitis, gastritis, gastroenteritis, and colitis - collectively termed eosinophilic gastrointestinal disorders (EGIDs)
- Patients with EGIDs have debilitating symptoms such as dysphagia, abdominal pain, nausea, vomiting, and diarrhea

Figure 1. Pathogenesis of EGIDs (Illustrative)

Eosinophilic gastritis (EG) and gastroenteritis (EGE) are EGIDs that affect 45,000 - 50,000 patients in the US, though this number may be significantly underdiagnosed
- Current treatment options such as diet restriction and corticosteroids have limited efficacy and/or are inappropriate for chronic use
- There is a significant medical unmet need for novel therapies

Figure 2. AK002 Mechanism of Action

Siglec-8
Inhibitory Receptor
- Selectively expressed on mast cells, eosinophils
- AK002 is an inhibitory receptor selectively expressed on human eosinophils (eos) and mast cells (MCs)
- Preclinical studies have demonstrated that anti-Siglec-8 monoclonal antibodies (mAbs) can deplete blood and tissue eosinophils and inhibit mast cell activity
- While the role of eosinophils in EGIDs have been examined in murine models, the function of mast cells in EGIDs has not been studied
- This study examined the activity of an anti-Siglec-8 mAb, murine AK002, in a mouse eosinophilic gastritis & gastroenteritis model

METHODS

- Anti-Siglec-8 mAb Reduces Eosinophilic Gastritis and Gastroenteritis
- Schematic of Siglec-8 expression in gastric tissues showing significant eosinophil infiltration in gastric tissue
- AK002 was dosed at 0, 50, 150, and 500 µg/mouse IV intraperitoneally daily
- Mice challenged with OVA
- Anti-Siglec-8 mAb treated mice displayed significantly reduced eosinophil infiltration in the stomach & small intestine

RESULTS

- Anti-Siglec-8 mAb treated mice displayed significantly reduced eosinophil infiltration in the mesenteric lymph nodes (MLNs)
- Significant depletion of blood eosinophils was seen in anti-Siglec-8 mAb treated mice

CONCLUSIONS/DISCUSSION

- Sanitation and intragastric challenge with OVA induced eosinophil and mast cell infiltration in the stomach and small intestine representing a model of EG and EGE
- The infiltration of both eosinophils and mast cells in GI tissue suggests that both cell types may induce EG and EGE disease pathogenesis
- Therapeutic treatment with anti-Siglec-8 mAb significantly reduced stomach and small intestinal eosinophils and mast cells
- Consistent with the reduction of eosinophils and mast cells, anti-Siglec-8 mAb significantly decreased OVA-induced intestinal inflammation
- These data provide support for the evaluation of an antibody to Siglec-8 in patients with EGIDs and other eosinophilic and mast cell driven diseases

Figure 3. Siglec-8 Expression in Transgenic Mice

Figure 4. Eosinophilic Gastritis and Gastroenteritis Model

Figure 5. Flow Cytometry Gating Strategies in GI Tissue

Figure 6. Sensitization and Intragastric Challenge with OVA Induces Eosinophil and Mast Cell Infiltration in Stomach

Figure 7. Anti-Siglec-8 mAb Reduces OVA-Induced Eosinophil Infiltration in the GI Tract

Figure 8. Anti-Siglec-8 mAb Reduces Eosinophilic Infiltration in the MLNs and Decreases Blood Eosinophils

Figure 9. Anti-Siglec-8 mAb Reduces OVA-Induced Mast Cell Accumulation in Stomach and Small Intestine

Figure 10. Anti-Siglec-8 mAb Reduces Expression of Inflammatory Mediators in Small Intestine

Figure 11. Anti-Siglec-8 mAb Reduces OVA-Induced Cytokines and Chemokines in Serum

References:
- Bernal A, et al. CD45 promotes the infiltration of both eosinophils and mast cells in EGIDs. Allergy. 2017;
- Kappelman MD, et al. CD45 promotes the infiltration of both eosinophils and mast cells in EGIDs. Gastroenterology. 2015;