

## Public Abstract

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**Introduction:** Feline allergic asthma is a common lower airway disease that has a complex underlying immunopathogenesis. Current therapeutic mainstays (glucocorticoids, bronchodilators) do not address the underlying immune regulatory dysfunction. Several new immunomodulators have been recently investigated in experimental models and clinical studies of allergic disease. The aim of this thesis was to review the immunomodulators that have been previously evaluated in feline asthma and to specifically evaluate the immunomodulator, FeG-COOH (FeG), in an experimental model of feline asthma.

Our laboratory previously evaluated the effect of a single dose of FeG on eosinophilic airway inflammation when given prior to an allergen challenge in experimentally asthmatic cats. While this single dose partially blunted airway inflammation compared with placebo, this therapy needed to be tested with more chronic use, given that exposure to allergen in pet cats is an unpredictable event. We hypothesized that a chronic (2 week) course of FeG in experimentally asthmatic cats would decrease airway inflammation and clinical signs of asthma.

**Methods:** Experimental asthma was induced in 10 cats using Bermuda grass allergen (BGA) and cats were randomly selected to receive either FeG (1 mg/kg, PO) or saline for 2 weeks, followed by a 2 week washout period. Cats then received the alternate treatment. Cytologic examination of bronchoalveolar lavage fluid (BALF) was used to document the development of an asthmatic phenotype prior to enrollment into the study (this disqualified one cat from the study). Aerosol challenge with BGA was performed weekly throughout the study. A clinical scoring system to evaluate clinical signs associated with the asthmatic phenotype, was employed prior to and after each 2 week treatment. Similarly, BALF and blood were collected prior to and after each of the 2 week treatment periods. Cytology and cytokine analysis were performed on BALF samples and in vitro cytokine restimulation was performed on peripheral blood mononuclear cells (PBMCs).

**Results:** There was no significant difference between the treatment groups in BALF total nucleated cell counts or eosinophil percentages. Greater than 40% of the BALF supernatant samples had IL-1, IL-4, IL-6, CXCL-8 (formerly IL-8) and IFN- $\gamma$  concentrations below the lower limit of detection of the assay regardless of time point or treatment administered. Interleukin-4 and IFN- $\gamma$  concentrations in the cell culture supernatant from stimulated PBMCs were below the lower limit of detection for all samples. Due to the low number of samples that had detectable concentrations of IL-1, IL-4, IL-6, CXCL-8 and IFN- $\gamma$ , statistical analyses of this data was not meaningful. There was no significant difference in BALF or plasma TNF activity or clinical scores between treatment groups.

**Conclusions:** In cats with experimental asthma, daily use of FeG (2 weeks) during chronic aeroallergen exposure did not dampen eosinophilic airway inflammation, alter cytokine profiles in the plasma or BALF, or decrease clinical signs associated with allergen challenge. These results support that FeG at this dosage can not be recommended as monotherapy for the chronic treatment of allergic asthma in cats. Whether FeG has a role in the acute management of asthmatic attacks or in combination with other treatments in cats has yet to be determined.