

## 770 Long-term Safety of Medium- and High-Doses Mometasone Furoate/Formoterol Combination in Persistent Asthmatics: Analysis of Adverse Events Incidence, Plasma Cortisol, and Ocular Changes

J. Maspero<sup>1</sup>, H. Nolte<sup>2</sup>, I. Cherrez Ojeda<sup>3</sup>; <sup>1</sup>Fundación Cidea, Buenos Aires, ARGENTINA, <sup>2</sup>Schering Plough, Kenilworth, NJ, <sup>3</sup>RESPIRALAB Allergy, Respiratory & Sleep Center, Guayaquil, ECUADOR.

**RATIONALE:** The safety of long-term use of mometasone furoate/formoterol (MF/F) combination administered via metered dose inhaler (MDI) for treatment of asthma has not been elucidated. We report the results of a 1-year study undertaken to assess the effect of medium- and high-doses of MF/F on incidence of adverse events (AEs), plasma cortisol level and ocular changes.

**METHODS:** Subjects ( $\geq 12$  years) with persistent asthma treated with medium- to high-dose ICS were stratified by ICS dose and randomized in a 2:1 ratio MF/F: fluticasone/salmeterol (F/S) to twice-daily doses of either MF/F (200/10mcg; n=141), F/S (250/50mcg; n=68), MF/F (400/10mcg; n=130), or F/S (500/50mcg; n=65). The incidence and severity of AEs, plasma cortisol 24-hour area under the curve (AUC), changes in lens opacities classification system, and intraocular pressure were determined.

**RESULTS:** Both MF/F doses were well tolerated and associated with AEs of frequency and nature similar to those observed with F/S. No unusual or unexpected adverse events were observed. The most common treatment-related AE was headache (MF/F=4.3%; MF/F 400/10mcg=3.1%; F/S 250/50mcg=5.9%; F/S 500/50mcg=1.5%). Overall, 99 subjects (24.5%; MF/F 200/10mcg=28.4%; MF/F 400/10mcg=23.1%; F/S 250/50mcg=23.5%; F/S 500/50mcg=20.0%) reported treatment-related AEs. Compared with baseline, both MF/F and F/S caused a similar decrease in plasma cortisol 24-hour AUC. For subjects on medium-dose ICS, decreases were MF/F=6% and F/S=17%; on high-dose ICS, decreases were MF/F=31% and F/S=34%. Overall, the percentage of ocular events was low (2-6%) and similar for MF/F and F/S.

**CONCLUSIONS:** In patients with persistent asthma medium- or high-dose MF/F combination therapy was associated with safety and tolerability similar to those on F/S.

## 771 ASHMI Induced Long-lasting Tolerance to Allergen Exposure In An Asthma Model Is Interferon $\gamma$ , But Not TGF- $\beta$ Dependent

K. D. Srivastava, T. Zhang, N. Yang, H. A. Sampson, X. Li; The Mount Sinai School of Medicine, Pediatric Allergy & Immunology and The Jaffe Food Allergy Institute, New York, NY.

**RATIONALE:** Chronic allergic asthma is the result of a Th2- biased immune status. Current asthma therapies control symptoms in some patients, but a long lasting therapy has not been established. ASHMI, a Chinese herbal formula improved symptoms and lung function, and reduced Th2 responses in a controlled trial of patients with persistent moderate to severe asthma. We evaluated the persistence of post-treatment beneficial effects of ASHMI in a murine model of chronic asthma and immunological mechanisms underlying such effects.

**METHODS:** BALB/c mice sensitized intraperitoneally with ovalbumin (OVA) received 3 weekly intratracheal OVA challenges to induce airway hyperreactivity (AHR) and inflammation (OVA mice). Additional OVA mice were treated with ASHMI (OVA/ASHMI) or water (OVA/Sham) for 4 weeks, and then challenged immediately and eight weeks post-therapy. In other experiments OVA mice received ASHMI treatment with concomitant neutralization of IFN- $\gamma$  or TGF- $\beta$ . Effects on airway responses, cytokine and OVA-specific IgE levels were determined 8 weeks post therapy.

**RESULTS:** Prior to treatment, OVA mice exhibited AHR and pulmonary eosinophilic inflammation following OVA challenge, which was almost completely resolved immediately after completing treatment and did not re-occur following OVA re-challenge up to 8 wks post-therapy. Reduced allergen-specific IgE ( $P<0.001$ ) and Th2 cytokine levels ( $P<0.01-0.001$ ), and increased IFN- $\gamma$  levels ( $P<0.001$ ) also persisted at least 8 wks post-therapy. ASHMI effects were eliminated by neutralization of IFN- $\gamma$ , but not TGF- $\beta$ , during therapy

**CONCLUSIONS:** ASHMI induced long-lasting post-therapy tolerance to antigen-induced inflammation and AHR. Elevated IFN- $\gamma$  is a critical factor in ASHMI effects.

## 772 Effects of Omalizumab in Non-Allergic Asthma

P. S. Creticos<sup>1</sup>, S. S. Saini<sup>1</sup>, M. D. Scarupa<sup>2</sup>, S. L. Balcer-Whaley<sup>1</sup>, A. P. Bieneman<sup>1</sup>, J. T. Schroeder<sup>1</sup>; <sup>1</sup>Johns Hopkins Asthma and Allergy Center, Baltimore, MD, <sup>2</sup>Institute for Asthma and Allergy, Chevy Chase, MD.

**RATIONALE:** Omalizumab's ability to neutralize total IgE and thus reduce binding of allergen-specific IgE to receptors (Fc $\epsilon$ RI) on immune cells underlies its efficacy as an approved therapy for moderate-to-severe perennial allergic asthma. Whether omalizumab demonstrates similar efficacy in treating so-called non-allergic asthma (NAA) has not been elucidated.

**METHODS:** A double-blinded, placebo-controlled clinical trial was conducted comparing the clinical efficacy of omalizumab vs. placebo in subjects with moderate-to-severe NAA. Mechanistic experiments also evaluated changes in serum IgE and phenotypic/functional alterations in circulating basophils and dendritic cells (DC).

**RESULTS:** A database/advertising screen of 870+ adult asthmatics yielded 85 subjects ( $<10\%$ ) meeting initial criteria, 29 of who completed screening, with 8 (1%) qualifying for enrollment. All subjects had negative primary puncture skin test sensitivity/RASTs to perennial allergens (dust mite/cat/dog/cockroach); two demonstrated secondary reactivity to dust mite. Mechanistically, an expected rise in serum IgE (1.5-/6.4-fold) was observed in 2/4 subjects 4 months on omalizumab. DC and basophils from these subjects showed a  $>50\%$  decrease in Fc $\epsilon$ RI $\alpha$ . However, low serum IgE levels ( $<2/8$  IU) were not increased in the other two omalizumab subjects, nor were there discernable changes in Fc $\epsilon$ RI $\alpha$  expression. Placebo subjects (n=3) showed no drop in Fc $\epsilon$ RI $\alpha$ . Finally, no discernable changes were observed in basophil/DC function in any of the omalizumab-treated subjects.

**CONCLUSIONS:** This study demonstrates the difficulty in identifying a true subset of patients with the disease entity of NAA. Although expected shifts in cellular Fc $\epsilon$ RI $\alpha$  expression were evident, we observed no evidence of clinical benefit (symptoms/lung function/med usage/QOL) in NAA subjects treated with omalizumab.

## 773 Three Years of Specific Immunotherapy may be enough to treat respiratory allergy

S. Echechipía<sup>1</sup>, E. Arroabarren<sup>2</sup>, M. J. Alvarez-Puebla<sup>1</sup>, B. E. García<sup>1</sup>, S. Martín<sup>3</sup>, A. I. Tabar<sup>1</sup>; <sup>1</sup>Hospital Virgen del Camino, Pamplona, SPAIN, <sup>2</sup>Hospital Donostia, San Sebastian, SPAIN, <sup>3</sup>Clinical Research Department. ALK-Abelló, Madrid, SPAIN.

**RATIONALE:** Subcutaneous immunotherapy (SCIT) discontinuation is based on individual decisions, so we sought for differences in clinical efficacy due to its duration.

**METHODS:** 142 dust mite allergic patients under SCIT for 3 consecutive years (Pangramin Depot, ALK-Abelló) were randomly assigned for discontinuation (IT3, n=70) or for 2 additional SCIT years (IT5, n=72). 27 patients were included as controls. Efficacy was assessed by rhinitis and asthma clinical and medication based scores, visual analog scale (VAS), rhinitis (RQLQ) and asthma (AQLQ) quality of life questionnaires, skin tests and serum immunoglobulins before immunotherapy and at 3<sup>rd</sup> and 5<sup>th</sup> year.

**RESULTS:** Before immunotherapy, no differences were detected between SCIT patients. At 3<sup>rd</sup> year, significant rhinitis global score decreases were observed in IT3 (46%) and IT5 (54.6%). Asthma global scores were diminished significantly in IT3 (84%) and IT5 (75.2%). Significant differences were also detected in VAS, RQLQ and AQLQ scores in both groups. At 5<sup>th</sup> year no differences were observed between both groups in rhinitis ( $p=0.66$ ) and asthma ( $p=0.77$ ) scores, VAS ( $p=0.66$ ), RQLQ ( $p=0.32$ ) or AQLQ ( $p=0.88$ ). Specific IgG4 levels remained high in 5<sup>th</sup> year in IT5 group and were reduced in IT3 group. No other differences were detected between the 3<sup>rd</sup> and 5<sup>th</sup> year within the SCIT groups.

**CONCLUSIONS:** Three years of dust mite SCIT induces significant improvement in allergic rhinitis and asthma. The benefit of two additional years remains controversial.