

Eastern Allergy Conference

June 2-5, 2016 ~ Palm Beach, FL

All Scientific Posters will be on display in the South Ballroom Foyer, Friday, June 3rd and Saturday June 4th. Authors of these posters are requested to be at their poster to discuss their work from 9:45-11:00, both Friday and Saturday.

Not for
CME Credit

Increased Prevalence of Macrolide Allergy in Middle-Aged Women **

Jaison Jose, D.O

Purpose: The rates and demographics of macrolide allergy have not been well studied. We sought to investigate reactions to this medication utilizing our Electronic Medical Record (EMR).

Methods: After Institutional Review Board (IRB) approval for this project, we used the EMR available at Penn State Hershey Medical Center. We searched 427,653 patient charts from the calendar year 2014, and collected information about medication allergies, age, and gender.

Results: We identified drug allergies listed in 81,395/427,653 patients (19%). There were 150,121 medication allergies documented, as many patients had more than one allergy. Antibiotics accounted for 52,138 (35%) of allergies. Macrolides (5036, 9 % of allergenic drugs) were the third most common antibiotic allergy, behind penicillins and cephalosporins. There was a strong female predominance (77%). When stratifying by age, there was equal male:female ratios for the first two decades, but then female gender was associated with the majority of allergies. This peaked in the age range of 40-59 years in females, and then declined. The number of macrolide allergies in men was stable from the ages of 10-80 years.

Conclusions: Macrolides are commonly prescribed and the rates of allergy to this class of antibiotic increases steadily in females from puberty until middle age, while the rates of allergy in men are stable. We hypothesize that there may be a hormonal component that needs to be studied further. The risk of reaction to macrolides should be considered in women of between the ages of 20-60 years.

Benzocaine-Induced Methemoglobinemia **

Peter A. Ricketti, DO and Richard F. Lockey, MD

Introduction: Methemoglobinemia is an uncommon complication from topical benzocaine.

Methods: A 5 ½ year-old male presents to the clinic with a history of serious, life-threatening methemoglobinemia. At age 1 ½ years, while in daycare, he had benzocaine gel “rubbed” on a lesion in his mouth. Over the next hour he turned “blue”. He was transferred by EMS to a hospital where he was treated with methylene blue for methemoglobinemia. He never lost consciousness but did have trouble breathing and was “extremely blue”. He was discharged from the hospital 24 hours later without sequela.

Results: Methemoglobinemia is an elevated circulating fraction of methemoglobin within erythrocytes resulting from the conversion of a normal ferrous (Fe²⁺) ion into a trivalent ferric (Fe³⁺) ion.¹⁻³ Offloading of oxygen is impaired resulting in metabolic acidosis and in severe cases, death.⁴⁻⁵ Through 2013, there are 375 cases of methemoglobinemia associated with benzocaine and 16 associated with lidocaine.⁶ A search of the literature reveals no case reports in which another local anesthetic has been used in a patient with benzocaine or local anesthetic-induced methemoglobinemia. The etiology may be associated with an aniline ring structure in these medications. A definitive diagnosis requires a high methemoglobin and low oxygen saturation and oxyhemoglobin level.⁷ Treatment is intravenous methylene blue 1-2mg/kg over 5 minutes, not exceeding 7 mg/kg.⁸ Severe cases require hemodialysis or exchange transfusions.

Conclusion: Life-threatening benzocaine- and local anesthetic-induced methemoglobinemia is rare. Its etiology is unknown and the use of other local anesthetics in subjects with this disease is not recommended.

Management of granulomatous lymphocytic interstitial lung disease in a patient with common variable immune deficiency **

Mohini Pathria, MD, Daniel Urbine, Marc Zumberg, Juan Guarderas

Introduction: Common variable immune deficiency (CVID) results in low levels of most or all immunoglobulin classes, a defective host antibody response, and frequent bacterial infections. Granulomatous lymphocytic interstitial lung disease (GLILD) is a rare, non-infectious complication of CVID that significantly increases mortality risk in patients who have CVID. We describe the presentation of a patient with this condition and review the literature surrounding the diagnosis and management of GLILD.

Case: A 61-year-old woman with CVID presented with longstanding cough and progressive dyspnea and was diagnosed with GLILD. She was treated with subcutaneous immunoglobulin therapy. She became increasingly symptomatic and developed increased pulmonary infiltrates, pleural effusions, mediastinal adenopathy, splenomegaly, and pancytopenia. An interdisciplinary team composed of an immunologist, pulmonologist, and hematologist deliberated over a management approach.

Results: Computed tomography revealed worsening cervical, mediastinal, and hilar lymphadenopathy, bilateral pleural effusions, and lower lobe bronchiectasis with peribronchial thickening. There was marked splenomegaly and worsening retroperitoneal, periaortic, pelvic and inguinal lymphadenopathy. Several additional studies and procedures were completed in our patient to evaluate for lymphoproliferative disease. Transbronchial subcarinal node biopsy showed some atypical B cells. Bone marrow biopsy demonstrated normocellular bone marrow with no evidence of lymphoproliferative disorder and normal cytogenetics. Pleural fluid did not demonstrate clonal cell population. Retroperitoneal lymph node biopsy was negative for lymphoma and demonstrated scattered non-caseating granulomata.

Conclusion: The patient was diagnosed with GLILD and started on daily oral azathioprine therapy and rituximab infusions, administered each week for four weeks every 4-6 months and experienced dramatic improvement in her symptoms since initiation of therapy.

Hereditary Angioedema: Implications of Management in an Outpatient Setting *

Mohini Pathria, MD, Juan Guarderas

Introduction: Hereditary angioedema is a rare autosomal dominant disease characterized by recurrent episodes of edema of the subcutaneous tissue, gastrointestinal tract, and airway. Affected individuals have decreased production or dysfunction of the C1 inhibitor. Recently approved medications for hereditary angioedema have been effective in decreasing the morbidity and mortality of acute attacks among patients. We describe the presentation of a patient with this condition and explore limitations of implementing recommended therapy.

Case: A 38 year old woman was referred to the allergy clinic for recurrent angioedema. During childhood, she underwent a laparotomy for presumed appendicitis; however, her appendix was normal. She consequently developed episodes of lip, hand, and foot swelling, occurring about 2-7 times a month. During these episodes, she was treated with antihistamines and had limited symptom improvement. Her mother had similar attacks. She has no allergies or skin manifestations during the attacks. She has a normal physical exam.

Results: Laboratory studies show a total complement of <13 (normal 31-60), C4 level of <3 (normal 16-47), and C1 inhibitor level of 3 (normal 21-39). History and laboratory data confirmed the diagnosis of hereditary angioedema.

Conclusion: This patient underwent a long delay from onset of symptoms to diagnosis. Furthermore, while initiating therapy, neither medication nor protocols were available in the facility pharmacy. Ultimately, pharmaceutical companies were directly contacted and assisted in handling insurance and administration services. The process approximated 2 months from diagnosis to medication acquisition, causing further delay and discomfort for the patient from diagnosis to treatment. Further interventions to spread awareness of the condition and to increase support for affected patients and physicians managing this condition need to be implemented.

In hospital outcomes of Asthma exacerbation among HIV patients: Study from Nationwide inpatient sample (2001-2012) **

Banipreet Kaur, MD, Sohilkumar Manvar, MD, Badal Thakkar, MD, Elizabeth A. Secord, MD

Background: There are more than 1.2 million people in US with human immunodeficiency virus (HIV). Pulmonary disease is amongst the most common etiologies for hospitalization in this population cohort. Although the pulmonary infection rates have been on a decline since advent of highly active anti-retroviral therapy (HAART), contrarily more patients are admitted with non-infectious pulmonary issues like asthma and COPD. The primary objective of our study was to evaluate in hospital outcomes in HIV patients admitted with asthma exacerbations in terms of mortality, length of stay (LOS) and hospitalization cost.

Methods: We queried the HCUP's Nationwide Inpatient Sample (NIS) from 2001 to 2012 to identify patients, age \geq 18 years, using ICD-9 diagnosis code 493.0 for asthma (n=36,379). The NIS is a stratified sample designed to approximate a 20% sample of US community (nonfederal, short-term, general, and specialty) hospitals. Multivariate logistic regression analysis was used to evaluate predictors of in-hospital mortality, LOS and hospitalization cost.

Results: In hospital mortality was 0.5%. Mechanical ventilation (OR, 95 % CI, p-value) was a significant predictor of in-hospital mortality (97.4, 31.9-297.4, <0.001), LOS (4.3 \pm 0.4 days, 3.5-5.2 days, <0.001) and hospitalization costs (\$17,324 \pm 1,356, \$14,665-\$19,983, <0.001). A higher burden of baseline co-morbidities represented by a higher Charlson Co-morbidity Index (CCI) score posited longer LOS (1.1 \pm 0.2 days, 0.6-1.5 days, <0.001) and higher hospitalization costs (\$3,038 \pm 692, \$1,682-\$4,394, <0.001).

Conclusion: There is a significant increase in in-hospital mortality, LOS and hospitalization costs in HIV patients admitted with asthma exacerbation who require intubation/mechanical ventilation. LOS of hospitalization costs are also higher in patients with a higher burden of baseline co-morbidities.

Link With Allergic Rhinitis, Asthma and SLE **

Marianne Frieri, M.D., Ph.D. and Eric Sin MD

Introduction: Systemic lupus erythematosus (SLE) is a complex condition caused by complex interactions between genes, the environment, hormones, smoking, infections, drugs, and abnormalities of the adaptive immune system. It is characterized by aberrations that involve hyperactive B cells, T cells, cells of the monocytic lineage, resulting in polyclonal B cell activation, increased numbers of antibody producing cells, hypergammaglobulinaemia, autoantibody production, and immune complex formation. Th17 cells, can down-regulate the Th2 cells and have been implicated in the pathogenesis of SLE. Studies have shown that asthma and autoimmune disease, are associated, and increased incidence of antinuclear autoantibodies and detection of autoantibodies against either bronchial epithelial antigens or endothelial antigens in patients with nonallergic asthma suggest that the disease may have an autoimmune basis.

Case Description: We describe 49 year old Hispanic man with a history of SLE, diagnosed many years ago, Raynaud's, asthma, diagnosed in childhood, mental retardation, and depression pancreatitis who was referred to our allergy clinic for the evaluation of a generalized rash present for many years, unrelieved by various lotions and steroid creams. Physical examination revealed a bald male with multiple freckles throughout the body most prominent on the face, normal vital signs, erythematous turbinates and dermatitis of the lower extremity. RAST testing was performed and results are below. The patient was instructed to return to the clinic for results.

Results:
Birch 13.2 (class 3), C. Herbarum 3.9 (class 3), Cockroach 9.03 (class 3), Common Ragweed 52.1 (class 5), D. farina 3.97 (class 3), D. pteronyssinus 0.53 (class 1), Dog Dander 4.29 (class 3), Egg Mix 3.05 (Class 2), Giant Ragweed 41.2 (class 4), H. Braziliensis 9.98 (Class 3), June Grass >100 (class 6), Maple 14.7 (class 3), Mugwort 15.4 (class 3), Oak 14.6 (class 3), P. Notatum 3.28 (class 2) and Timothy grass >100 (class 6).

Discussion: Allergic rhinitis and asthma are both systemic inflammatory disorders with similar mechanisms with numerous cells and inflammatory mediators both involved in autoimmune disorders such as SLE. Autoimmune conditions and allergic diseases are both characterized by immune dysregulation. Asthma is a heterogeneous disorder characterized by chronic inflammation of the respiratory airways that can be triggered by allergen exposure or by other mechanisms, possibly autoreactive/autoimmune. Asthma and autoimmune diseases share the involvement of the immune system in both types of disorder. SLE is an autoimmune disease with a wide spectrum of disease expression. Clinical experience suggests that allergic signs and symptoms are more frequently observed in patients with SLE than in the general population.
Conclusion: This review used a case report and several articles on pub med to cover a link between several autoimmune disorders such as allergic rhinitis, asthma and SLE, a common autoimmune disorder.

Mobile Phone Asthma Action Plan Application; Use in Adolescents **

Laura Odum, DNP, FNP-BC

Background: Asthma burden affects mortality, morbidity, quality of life, and the economy. The *British Medical Journal* recently reported that two-thirds of asthma deaths are due to failure to follow recommended guidelines and primary care failings in routine care. Written asthma action plans are standard of care according to national guidelines, but these plans are seldom prescribed. Furthermore, these written care plans are often unavailable at the time of an exacerbation. The purpose of this project was to create an asthma action plan application for smartphones. The goal of the project was improved patient access to their asthma action plan and improved utilization rates among providers.

Methods: A development studio was consulted for support in developing a smartphone application to code the software for the asthma action plan and assist in the design process. Following development of the application, a survey was completed to evaluate design and functionality.

Results: All survey participants agreed that the application was easy to use, could be used without written instruction and was designed for adolescents with asthma of any severity. Patients and providers noted that the app would help provide information about what to do in the event of an asthma exacerbation and that the application would be used frequently.

Conclusions: There was consensus from both patients and providers that this application is not only functional but also helpful in the event of an asthma exacerbation. The project met the goal of creating a mobile phone application that improved patient access to asthma action plans.

Common Variable Immunodeficiency with Elevated IgM, Differential Diagnosis **

Chen Hsing Lin, MD¹ and Panida Sriaroon, MD²

Background: Common variable immunodeficiency (CVID) is a heterogeneous antibody deficiency. Typically, subjects with CVID have normal or low serum IgM. A high serum IgM (>1,000 mg/dL) is uncommon and warrants further investigation.

Case Presentation: A 55-year-old Caucasian female was diagnosed with CVID 6 years ago based on a history of recurrent sinusitis and a low serum IgG, undetectable IgA and absence of protective antibodies following pneumococcal polysaccharide immunization. Other associated conditions include diffuse pulmonary nodules, splenomegaly, and a granuloma in an eye muscle. She was misdiagnosed with sarcoidosis and treated with oral prednisone for several years. There was no associated fever, weight loss, or organ specific symptoms. She was subsequently evaluated for CVID and immunoglobulin replacement therapy initiated. The serum IgM level gradually increased over 3 years (peak 5,850 mg/dL; mean 1,400 mg/dL [normal range 40-230 mg/dL]).

Results: Serum and urine protein electrophoresis revealed an increased gamma globulin fraction and immunofixation was normal. An open lung biopsy was consistent with granulomatous and lymphocytic interstitial lung disease (GLILD). She also had impaired in vitro T cell proliferation, decreased class switched memory B cells with increased transitional B cells, and decreased B cell activating factor receptor expression. CD40 ligand and inducible T-cell co-stimulator expression after mitogen stimulation were normal. Genetic sequencing of activation-induced cytidine deaminase, lipopolysaccharide-responsive vesicle trafficking, beach- and anchor-containing, and cytotoxic T lymphocyte-associated protein-4 are pending to rule out hyper-IgM syndromes. Genetic testing for activated phosphoinositide 3-kinase δ syndrome (APDS), a latent onset hyper-IgM syndrome mimicking CVID, which is the suspected diagnosis is pending. The patient is scheduled to begin rituximab and azathioprine for GLILD.

Conclusions: This case highlights the importance of elevated IgM levels in subjects with CVID. APDS and other alternative diseases should be considered.

Alpha-gal allergy: a further look into other possible routes of transmission**

Gayatri Patel MD, Shahab Virani MD, Frederick Little MD

Introduction: Galactose-alpha-1-3-galactose (alpha-gal) allergy is a delayed reaction of 3-6 hours after pork, lamb or beef ingestion. Multiple tick species have been identified as likely vectors for alpha-gal transmission to humans who inherently lack this protein and can potentially develop hypersensitivity reaction. Without a clear tick bite history, it typically is excluded from the differential. This can, however, be misleading as other exposures can potentially induce alpha-gal allergy.

Case: 24 year old healthy Brazilian female without significant atopic history presented with recurrence of angioedema. History revealed no clear precipitant but possible aggravation by NSAID and meat consumption. She grew up in Brazil and had no history of tick bites. Moreover, there are no known tick species in Brazil that have been linked as a vector for transmission. She reports that cat exposure leads to allergic rhinitis symptoms. Alpha-gal and cat dander IgE were positive while dog, beef and pork IgE were negative.

Discussion: There is a strong association with alpha-gal IgE production related to tick exposure. Limited evidence exist to support other routes of sensitization. Cat exposure has been suggested as a means since cat dander has the alpha-gal epitope that could theoretically lead to sensitization through airborne exposure. This case captures the challenge of physicians identifying those at risk for alpha-gal allergy if there is no tick exposure history and adds support that cat exposure could lead to sensitization of which its clinical significance remains to be elucidated.

Constructivist Based Online Group Asthma Education Program **

Stuart Tousman, Ph.D., Lisa Johnson, RRT, Christina Blankenship, RN.

Introduction: The purpose of the present program was to design, implement, and evaluate a new online group based asthma education program. The design of the program was based on Vygotsky's constructivist teaching model in which the teachers assess the learners' zone of proximal development and then engage the learners in interactive scaffolding based activities to enhance learning.

Method: Ten participants engaged in six asynchronous one month modules on key asthma topics (medications, exercise, mind/body, behavior change, allergies). The modules were divided into two phases. In phase I (2 weeks), the instructor posted stimuli designed to elicit conversation about asthma. These stimuli included brief article abstracts and handouts with open ended threaded discussion board questions that asked participants to discuss the stimuli and to relate the information to their own asthma experiences. In phase II (2 weeks), the instructor recorded two brief acoustic lectures (5-10 minutes each) in which he elaborated on the phase I discussions by adding in evidence based asthma guideline information.

Results: The average number of participant posts per module was 20 and the average number of participant views per module was 170. Program evaluations indicated that participants enjoyed the interactive design of each module and they learned a great deal from the faculty and other participants.

Conclusions: In future programs we hope to train healthcare providers how to implement our group based online constructivist based educational program so that adults and caregivers may learn more about asthma self-management.

Dose-Ranging Efficacy and Safety Study of Albuterol Multidose Dry Powder Inhaler (MDPI) vs Albuterol Hydrofluoroalkane (HFA) and Placebo MDPI in Children With Asthma **

Paul Y Qaqundah, MD¹; Herminia Taveras, PhD, MPH²; Harald Iverson, PhD²

Introduction: Dose-ranging efficacy and safety study to evaluate albuterol MDPI and albuterol HFA relative to placebo in children with persistent asthma.

Methods: A phase 2, multicenter, double-blind, double-dummy, single-dose, 5-period, crossover study (ABS-AS-202; NCT01899144) randomized children (aged 4–11 years) with persistent asthma and prestudy forced expiratory volume in 1 second (FEV₁) of 60%–90% of predicted to 1 of 10 treatment sequences containing albuterol MDPI (90 and 180 mcg), albuterol HFA (90 and 180 mcg), and placebo MDPI+placebo HFA. Efficacy was evaluated by measuring area under the baseline-adjusted percent-predicted FEV₁-time curve over 6 hours postdose (PPFEV₁AUC₀₋₆); safety was evaluated by adverse events.

Results: The full analysis set included 61 patients. Albuterol MDPI and albuterol HFA significantly improved PPFEV₁AUC₀₋₆ vs placebo ($P \leq 0.0107$). Improvement in PPFEV₁AUC₀₋₆ vs placebo with albuterol MDPI 90 and 180 mcg was similar (21.2±4.87 [95%CI 11.60,30.81] and 22.6±4.87 [95%CI 13.00,32.20] %•hour, respectively). Improvement with albuterol HFA 180 mcg was significantly ($P=0.0226$) greater vs albuterol HFA 90 mcg (23.7±4.85 [95%CI 14.13,33.23] and 12.5±4.85 [95%CI 2.93,22.05] %•hour, respectively). All doses of albuterol were generally well tolerated.

Conclusions: Albuterol MDPI significantly improved pulmonary function vs placebo in children with asthma. Improvements for albuterol MDPI 90 and 180 mcg were similar; a dose-response effect was observed with albuterol HFA. Results suggest that relief of asthma symptoms in children may be managed adequately with albuterol MDPI (1–2 inhalations). No new safety concerns were noted with albuterol MDPI, and its safety profile is consistent with that of albuterol HFA.

Supported by Teva Pharmaceuticals

Efficacy and Safety of Albuterol Multidose Dry Powder Inhaler (MDPI) Versus Placebo in Children With Asthma **

Craig LaForce, MD, CPI¹; Herminia Taveras, PhD, MPH²; Harald Iverson, PhD²

Introduction: A chronic-dose study of the efficacy and safety of albuterol MDPI in children with asthma.

Methods: This phase 3, double-blind, parallel-group, multicenter, 3-week study (ABS-AS-303; NCT02126839) included children (aged 4–11 years) with asthma and prestudy forced expiratory volume in 1 second (FEV₁) of 50%–95% of predicted. After a 14-day run-in period during which patients continued their current asthma therapy and received single-blind placebo MDPI, patients were randomized to albuterol MDPI, 90 mcg/inhalation, 2 inhalations 4 times daily (total daily dose, 720 mcg), or placebo for 3 weeks. Pulmonary function testing occurred on treatment day 1 (TD1) and 22 (TD22). Efficacy and safety were evaluated by measuring area under the baseline-adjusted percent-predicted FEV₁ time curve over 6 hours postdose (PPFEV₁ AUC₀₋₆) and adverse events.

Results: The full analysis set included 184 patients. Albuterol MDPI-treated patients experienced significantly ($P < 0.0001$) greater improvements in PPFEV₁ AUC₀₋₆ over the 3-week study versus placebo recipients (least squares mean difference of 25%•h in favor of albuterol); improvements were similar on TD1 and TD22 for albuterol MDPI-treated patients and greater than placebo ($P < 0.001$). Albuterol benefits (mean change in PPFEV₁) were evident 5 minutes postdosing and lasted several hours; (maximal effect, 1–2 hours postdose). Albuterol MDPI was well tolerated.

Conclusions: Albuterol MDPI, administered chronically for 3 weeks, improved pulmonary function in pediatric patients significantly better than placebo with similar improvements on TD1 and TD22. Clinical effects were evident 5 minutes postdose and were maintained for >2 hours. Four-times-daily administration was generally well tolerated.

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Asthma Inhaler Misuse: Clinical Impact of Asynchrony in Patients with Asthma Using a Metered Dose Inhaler **

Agnes S Sundaresan, MD, MPH; Jasmina Ivanova, MA; Howard Birnbaum, PhD; Thomas Ferro, MD; Ruchir Parikh, PharmD

Introduction: A common error among asthmatics using metered dose inhalers (MDI) is asynchrony, a lack of coordination between the start of inhalation and actuation of a dose. Asynchrony can reduce lung deposition of medications and decrease treatment effectiveness. Real-world research regarding the association between asynchrony and clinical outcomes is limited. This study assessed this relationship among asthmatics on controller MDIs.

Methods: Patients (n=254) were identified via electronic health records. Their data was collected at Geisinger Health System. Patients were ≥ 12 years old, had ≥ 1 asthma exacerbation and no COPD diagnosis, ≥ 2 prescriptions for inhaled corticosteroid alone or with long-acting $\beta 2$ agonist MDI, and no nebulizer use. Nurses used a standardized, 10-step checklist to evaluate inhaler technique using a placebo MDI. Asynchrony was defined as having any gap between breathing in and actuation. Patients were classified as error-prone (n=32) or not error-prone (n=222). Comparisons of outcomes were conducted using multivariable regression analyses controlling for age, gender, asthma severity and baseline comorbidities.

Results: Mean cohort age was 49.3 years and 92.9% were white. Asynchrony was significantly associated with higher odds of an asthma exacerbation (adjusted odds ratio [OR] 2.99 (1.31-6.82), $p=0.0090$) and lower odds of risk domain asthma control (adjusted OR=0.41 (0.17-0.95), $p=0.0367$). Medical costs were higher in the error-prone cohort but not statistically significant.

Conclusions: This study provides real-world evidence that asynchrony among asthma patients using MDIs is associated with worse clinical outcomes, including higher odds of an asthma exacerbation and lower odds of achieving risk domain asthma control.

Supported by Teva Pharmaceuticals

Asthma Inhaler Misuse: Assessment of Inhaler Technique in Patients with Asthma Using a Metered Dose Inhaler **

Agnes S Sundaresan, MD, MPH; Wendy Y Cheng, MPhil, MPH; Howard Birnbaum, PhD; Thomas Ferro, MD; Ruchir Parikh, PharmD

Introduction: Improper use of metered dose inhalers (MDIs) is common among asthma patients. Some inhaler technique errors are deemed "critical" and likely compromise the benefits patients would otherwise receive from their medication. This study assessed the prevalence of inhaler technique errors among asthmatics in a primary care population receiving controller MDIs.

Methods: Patients were assessed in-person at Geisinger Health System (Pennsylvania). They were ≥ 12 years old, had ≥ 1 asthma exacerbation and no COPD diagnosis, ≥ 2 prescriptions for an inhaled corticosteroid alone or with long-acting $\beta 2$ agonist MDI, and no nebulizer use. Nurses used a standardized, 10-step checklist to evaluate inhaler technique using a placebo MDI. Four definitions of "errors" were considered: [1] Asynchrony: Having a gap between breathing in and actuation. [2] Shake inhaler: Failing to shake inhaler for ≥ 5 seconds. [3] Any error: Having an error in any of the 10 steps. [4] Any error in a critical step: Having an error in any of 7 "critical" steps.

Results: Patients evaluated (n=254) had a mean age of 49.3 years, were 35% male, 93% white and 71% with moderate persistent asthma. Results showed that 32 patients (12.6%) demonstrated asynchrony, 107 patients (42.1%) failed to shake the inhaler, 197 patients (77.6%) demonstrated at least 1 error, and 187 patients (73.6%) performed a critical step error.

Conclusions: This study provides clinical evidence that multiple errors can occur in MDI use. The majority of primary care asthma patients displayed some form of improper inhaler technique when using an MDI.

Supported by Teva Pharmaceuticals

Association between Early Improvements in Lung Function and Asthma Control with Reslizumab and the Annual Rate of Asthma Exacerbations*

E.D. Bateman¹, J. Zangrilli², M. Germinaro², S. Weiss³ and M. Castro⁴

Rationale: In patients with severe asthma and elevated blood eosinophils, reslizumab, a humanized anti-interleukin-5 monoclonal antibody, reduced asthma exacerbations and improved forced expiratory volume in 1 second (FEV₁) and asthma control questionnaire-6 (ACQ-6) scores. This analysis examined the relationship between early improvements in lung function and asthma symptoms and the frequency of asthma exacerbations.

Methods: Data were pooled from two placebo-controlled trials of reslizumab 3.0mg/kg (every 4 weeks) in patients aged ≥ 12 years with a screening blood eosinophil count $\geq 400/\mu\text{L}$ who were inadequately controlled on an inhaled corticosteroid-based regimen (Castro Lancet Res Med 2015). Analysis of frequencies of asthma exacerbations during the 52-week treatment period were stratified by the presence of an early (up to week 16) FEV₁ ($\geq 100\text{mL}$) or ACQ-6 (≥ 0.5 units) response.

Results: Patients were randomized to placebo (n=476) and reslizumab (n=477). The proportion of reslizumab patients having an FEV₁, ACQ-6, or 'FEV₁ or ACQ-6' response by week 16 was 58%, 71%, and 83%, respectively; the corresponding exacerbation rate reductions vs placebo were 71%, 61%, and 60%. Exacerbation rate reductions for FEV₁, ACQ-6, or 'FEV₁ or ACQ-6' non-responders were 25%, 36%, and 26%, respectively. Larger absolute increases in FEV₁ with reslizumab were associated with larger reductions in asthma exacerbation rate.

Conclusion: Early improvements in lung function or symptoms occurred in a majority of reslizumab-treated patients and were associated with substantial reductions in the annual rate of asthma exacerbations; this association was not shown with placebo. This information may be useful to healthcare providers evaluating reslizumab therapy.

Sponsor: Teva Pharmaceuticals Inc.

No Significant Growth Velocity Changes in Two Trials Evaluating the Potential Effects of Flunisolide HFA on Growth in Pediatric Patients with Mild-to-Moderate Asthma **

Renee Bomar, MSN, CPNP¹; David Skoner, MD²

Introduction: Two 1-year clinical trials were performed with flunisolide HFA (Aerospan[®]), a small-particle inhaled corticosteroid with a built-in spacer, approved for the treatment of asthma in patients 6 years and older. Post-hoc analyses evaluated height changes and growth velocity changes from baseline after 52 weeks of treatment with flunisolide HFA 160 mcg BID (max approved dose in children 6 to 11).

Methods: The first study was a double-blind, randomized 1-year safety study of flunisolide HFA and placebo in children 4 to 9 with mild-to-moderate asthma (n=218). The second study was an open-label, randomized, 1-year safety study of flunisolide HFA, inhaled beclomethasone (BDP) CFC, and inhaled cromolyn (negative control) in children 4 to 11 with mild-to-moderate asthma (n=206). Each study was analyzed similarly for growth velocity (via stadiometry assessments) over 1 year.

Results: In the double-blind study, mean growth velocity was 6.01 cm/yr for flunisolide HFA versus 6.19 cm/yr for placebo, a non-significant difference ($p=0.425$). Distribution in height changes and growth velocity changes were similar between flunisolide HFA and placebo. In the open-label study, mean growth velocity was 6.2 cm/yr for the flunisolide HFA group versus 5.3 cm/yr for the BDP group ($p=0.008$) and 6.9 cm/yr for the cromolyn group ($p=0.254$). Distribution of height changes and growth velocity changes was similar between flunisolide HFA and cromolyn.

Conclusion: Two 1-year trials demonstrated that flunisolide HFA did not result in significant growth suppression in pre-pubescent pediatric asthma patients 4 to 11 years of age when compared to placebo or negative control.

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Efficacy of MP-AzeFlu (Dymista) by Allergy Season and Symptom Severity**

Ellen Sher, MD¹; Bruce Prenner, MD²; Alison Martens, RN, CNCP³; Stanley Goldstein, MD¹

Introduction. MP-AzeFlu (Dymista), a novel single-spray intranasal formulation of fluticasone propionate (FP) and azelastine hydrochloride (AZE) was proven effective for treatment of SAR vs FP and AZE alone in clinical studies conducted during different allergy seasons in the US. This analysis compares study results across seasons and by symptom severity.

Methods. A total of 4022 patients 12 years and older with moderate-to-severe SAR were randomized into four double-blind, placebo-controlled trials conducted during spring, spring/summer, fall, and Texas Cedar allergy seasons. Patients received MP-AzeFlu (50 µg FP/137 µg AZE per spray), FP (50 µg/spray), AZE (137 µg/spray) or placebo 1 spray/nostril bid. The primary efficacy variable was change from baseline in the 12-hr reflective total nasal symptom score (rTNSS). The median value for baseline rTNSS (18.9) was used to divide the study populations for subgroup analysis by severity, i.e. patients with baseline rTNSS >18.9 (more severe) and ≤18.9 (less severe).

Results. MP-AzeFlu significantly improved rTNSS compared to FP and AZE in all studies. The response to MP-AzeFlu was consistent across the different allergy seasons, with an overall change from baseline in rTNSS of -5.3 (Texas Cedar), -5.6 (spring), -5.5 (fall), and -5.5 (spring/summer) in each study. In the Texas Cedar study, among less severe patients the relative difference to MP-AzeFlu was 42% vs FP (P=.019) and 64% vs AZE (P<.001), which increased to 49% vs FP (P=.044) and 70% vs AZE (P<.01) among more severe patients.

Conclusions. MP-AzeFlu provided consistent relief of nasal allergy symptoms compared to FP and AZE, regardless of allergy season or symptom severity.

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In vitro Determination of the Robustness of the Emitted Dose of Flunisolide HFA pMDI

Alexander D'Addio, PhD¹; David Skoner, MD²

Introduction: The current experiments were designed to determine the robustness of the aerosol characteristics of the delivered dose of flunisolide HFA (Aerospan 80 µg) compared to beclomethasone (QVAR 80 µg) both with and without holding chamber when used according to the prescribing information.

Methods: Actuation was simultaneously with sampling (simulated inhalation) or 1, 2, or 3 sec after sampling to mimic inhalation. The test drugs were administered through an Alberta idealized throat model with a realistic flow profile (30 L/min) generated by a Copley BRS3000 breathing simulator. The amount of drug deposited on the actuator/spacer, the throat, and the filter of the aerosol sampler was determined by HPLC analysis.

Results: Aerospan provided higher amount of drug on the filter than QVAR and achieved the labeled dose (80 µg) when sampled simultaneously with actuation. The amounts of flunisolide reaching the filter/percent of labeled dose were: 78.3 µg/97.9% when actuated simultaneously with sampling, 70.1 µg/87.6% at 1 sec after, 66.0 µg/82.5% at 2 sec after, and 68.3 µg/85.4% at 3 sec after sampling. QVAR did not achieve the labeled dose (80 µg) with simultaneous actuation (55.5 µg/69.4%) or at any interval thereafter. The percentage of drug recovered on the throat relative to the emitted (ex-valve) dose was 5.8% or lower for Aerospan compared to 17.6% or higher for QVAR.

Conclusions: When inhalation is performed as instructed by the prescribing information the amount of drug on the filter is higher with Aerospan than with QVAR, suggesting a potential higher lung deposition with Aerospan.

Sponsored by Meda Pharmaceuticals

Efficacy of MP-AzeFlu in the Treatment of Postnasal Drip and Rhinorrhea in Patients with Seasonal Allergic Rhinitis (SAR) **

Ellen Sher, MD¹; Alison Martens, RN, CNCP²; Stanley Goldstein, MD³

Introduction: The objective of this analysis was to evaluate MP-AzeFlu (Dymista), an intranasal formulation of azelastine HCL (AZE) and fluticasone propionate (FP) in a single delivery device, for the treatment of postnasal drip (PND) and rhinorrhea in patients with SAR.

Methods: A total of 3389 patients with PND and 3392 with rhinorrhea were analyzed from three 2-week, double-blind, placebo- and active-controlled studies comparing MP-AzeFlu to FP and AZE monotherapy. Treatments were administered 1 spray per nostril bid (AM and PM); total daily doses of FP and AZE were 200 mcg and 548 mcg, respectively. The primary efficacy variable was change from baseline in the 12-hour reflective total nasal symptom score (rTNSS), which included nasal congestion, sneezing, itchy nose, and rhinorrhea scored twice daily (AM and PM) on a 4-point (0-3) scale. Change from baseline in PND was evaluated in a similar pre-specified analysis.

Results: MP-AzeFlu was statistically superior (P<.05) to FP, AZE, and placebo for improving overall rTNSS in all studies. MP-AzeFlu was also statistically superior to FP (P<.05) and AZE (P≤.001) for improving PND and rhinorrhea in a meta-analysis of the three studies. Statistical or numerical improvements favoring MP-AzeFlu vs. FP and AZE were seen on each day of the 14-day study periods for each nasal symptom.

Conclusions: Results of these analyses demonstrated that MP-AzeFlu significantly improved the overall complex of nasal symptoms of SAR, including PND, compared to monotherapy with either FP or AZE.

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Exacerbation-free Asthma in Children Treated with Omalizumab*

Stanley Szeffler¹, Benjamin Trzaskoma², Brandee Paknis³, Benjamin Ortiz³, Evgeniya Antonova²

Introduction: Staying exacerbation-free allows children with asthma to enjoy a high quality of life and fully engage in age-appropriate activities. Omalizumab efficacy in children with IgE-mediated asthma was assessed in a 52-week, randomized, double-blind, placebo-controlled clinical trial. The rate of clinically severe exacerbations was decreased by 50.5% with omalizumab treatment compared to placebo. The proportion of children treated with omalizumab who remain exacerbation-free has not been previously reported.

Methods: Children ≥6 to <12 years old with asthma, inadequately controlled despite treatment with ≥200 µg/day fluticasone propionate or equivalent, were randomized to placebo or omalizumab (75-375 mg) every 2 or 4 weeks. During study weeks 1-24, patients received constant background inhaled steroid therapy, which could be reduced during weeks 25-52. We compared the percentage of children (omalizumab vs. placebo) who were free of clinically-significant exacerbations (worsening symptoms requiring doubling of baseline inhaled corticosteroid dose or systemic corticosteroids), any clinician-reported exacerbations, and severe exacerbations (required systemic corticosteroids and had a peak expiratory flow or FEV1 <60% of personal best) during weeks 1-52. P-values were based on Chi-Square test.

Results: 576 children included in the efficacy evaluation received omalizumab (n=384) or placebo (n=192). During weeks 1-52, 52.9% omalizumab vs. 39.6% placebo patients were free of clinically significant exacerbations (p=0.003), 25.3% vs. 13.0% were free of any clinician-reported exacerbation (p <0.001), and 88.0% vs. 79.2% were free of severe exacerbations (p=0.005).

Conclusion: Children with IgE-mediated asthma were more likely to be exacerbation-free if they received omalizumab than placebo.

Sponsored by Genentech/Novartis

My Hives Diary: An iOS App to Track Urticaria Symptoms *

Evgeniya Antonova, MS, PhD; Karina Raimundo, MS

Introduction: Chronic urticaria may burden patient lives through symptoms such as itch, hives, and angioedema. Patients may benefit from an electronic tool to track urticaria symptoms and their impact on daily activities and sleep.

Methods: The contents of MyHivesDiary are based on the Urticaria Patient Daily Diary (UPDD). UPDD was developed to collect symptoms and their impact in patients with chronic idiopathic/spontaneous urticaria (CIU/CSU) enrolled in Phase III clinical trials.

Results: MyHivesDiary is an iOS app suitable for iPhone or iPad. Daily, users can record: itch severity, number of hives, size of largest hive, presence of angioedema, interference with daily activities or sleep, and events pertaining to their urticaria. MyHivesDiary generates daily or weekly reports (graphs and numeric values). Daily reports include daily scores (Urticaria Activity Score, Itch Severity Score, Number of Hives Score, Largest Hive Score, Angioedema Occurrence, Interference with Activities Score, Interference with Sleep Score) and urticaria events. Weekly reports include weekly scores (calculated as a 7-day sum of the daily scores listed above; 7-day sum of UAS or UAS7) and daily events (in the last 1, 3, or 6 months). Users may choose to email reports in PDF format. Data are stored on user iOS device only. MyHivesDiary is available on iTunes store via the following URL: <https://itunes.apple.com/us/app/my-hivesdiary/id1008545433>.

Conclusions: MyHivesDiary is a convenient electronic tool for users to track urticaria symptoms, how urticaria affects their lives, and events associated with urticaria.

Sponsored by Genentech/Novartis

Demographic and Clinical Characteristics of Children and Adolescents with Severe or Difficult-to-Treat Asthma **

B. Chipps¹, T. Haselkorn², D.R. Mink³, S.J. Szeffler⁴

Introduction: TENOR is an observational study that provides unique insights into severe or difficult-to-treat asthma in children as young as 6 years of age.

Methods: 1,261 patients were stratified by baseline age group (6-8, 9-11, 12-14, 15-17 years). The chi-square test for categorical variables and ANOVA for continuous variables were used to identify significant differences among age groups, stratified by gender.

Results: Most patients had moderate (55%) or severe (41%) asthma by physician assessment. Of those using ≥ 3 long-term controllers (62%), in the previous three months 53% of children and 44% of adolescents reported a corticosteroid burst and 25% of children and 19% of adolescents had an emergency department visit. Past intubation was reported by 10% and 15% of children and adolescents, respectively. Medications used were: short-acting beta-agonists 96%, inhaled corticosteroids 95%, long-acting beta-agonists 74%, anti-leukotrienes 73%, systemic corticosteroids 15%, anticholinergics 10%, methylxanthines 8%, and cromolyn or nedocromil 9%. In females, weight for age ranged between the 67th-70th percentiles; height for age was between the 42nd-54th percentiles and was different among age groups ($p < .01$). Loss of lung function with age was seen: pre-bronchodilator FEV₁/FVC, males, went from 0.81 (6-8 years) to 0.73 (15-17 years), $p < .05$; females went from 0.84 (6-8 years) to 0.77 (15-17 years), $p < .05$.

Conclusions: Children and adolescents in TENOR demonstrated high rates of healthcare utilization and loss of lung function, despite using multiple long-term controllers. Asthma treatments that prevent loss of lung function and reduce healthcare resource use are needed for these patients.

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Predominance of Atopic Asthma in Patients with Severe or Difficult-to-Treat Asthma in the TENOR II Cohort *

L. Borish, S. J. Szeffler, B. Paknis, S.T. Weiss⁴, B.E. Chipps

Rationale: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens evaluated patients with severe or difficult-to-treat asthma (TENOR I). TENOR II assessed long-term outcomes in this cohort.

Methods: TENOR II (n=341) was a prospective, multicenter observational study with a single follow-up assessment >10 years after TENOR I. Atopic asthma was defined as having ≥ 1 positive specific-IgE test (≥ 0.35 kU/L). Clinical measures of atopic and non-atopic asthma patients were examined, as well as very poorly controlled (VPC) asthma based on National Heart, Lung, and Blood Institute asthma guidelines.

Results: Of 317 patients with a specific IgE measure, the majority (n=231; 72.9%) had atopic asthma; 86 (27.1%) had non-atopic asthma. IgE geometric mean was 130.7 IU/mL and 14.1 IU/mL for atopic and non-atopic cohorts, respectively. The most common positive IgE tests for atopic patients were perennial aero-allergens: cat dander (59.7%), dog dander (53.7%) and *Dermatophagoides farina* dust mite (43.7%). Mean (SD) blood eosinophil count for atopic and non-atopic groups were 201/ μ L (143) and 198/ μ L (147), respectively. Atopic and non-atopic patients were as likely to report any asthma exacerbation (defined as hospitalization/ER visit for exacerbations requiring corticosteroids) in the prior three months [24.7% (57/231) and 26.7% (23/86), respectively]. Over half (52.0%; 115/221) of atopic patients had persistent VPC asthma (VPC at TENOR I and TENOR II) versus 45.8% (38/83) of non-atopic patients.

Conclusions: Atopic asthma was highly prevalent and more frequent than non-atopic asthma in TENOR II; however frequency of exacerbations and level of control were generally similar between the two subgroups.

Supported by Novartis

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens: More than Decade Follow-up (TENOR II)*

B.E. Chipps, B. Paknis, S.J. Szeffler, S.T. Weiss⁴, R.S. Zeiger

Background: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) provided important insights into severe or difficult-to-treat asthma. TENOR II assessed long-term outcomes of these patients >10 years after TENOR I.

Methods: TENOR II was a multicenter observational study with a single, cross-sectional follow-up visit. Overall, 1,230 TENOR I patients were available for enrollment at sites that participated in TENOR II. Clinical and patient-reported outcomes were determined, including the percent of patients with very poorly controlled (VPC) asthma based on the National Heart, Lung, and Blood Institute asthma guidelines.

Results: A total of 341 (27.7%) patients enrolled in TENOR II. Demographic and clinical characteristics of TENOR II cohort were representative of TENOR I cohort. Mean percent predicted pre- and post-bronchodilator FEV₁ were 72.7% (21.5%) and 78.2% (20.7%), respectively. A total of 231/317 (72.9%) tested positive for ≥ 1 allergen specific IgE. Total IgE geometric mean was 72.2 IU/mL. Mean blood eosinophil count was 200/ μ L (144) (min, max: 0, 800). Mean FeNO was 29.1 (28.8) parts per billion (ppb) (min, max: 5, 272.5). A total of 88/341 (25.8%) patients experienced any asthma exacerbation in the prior 3 months. Over half (197/339; 58.1%) had VPC asthma.

Conclusions: TENOR II provides a representative sample of TENOR I with important longitudinal data >10 years after TENOR I to further characterize disease progression and heterogeneity. Current findings showed continued morbidity, including high levels of healthcare utilization and allergic disease, compromised lung function, and VPC asthma.

Supported by Novartis

Dupilumab Suppresses Fractional Exhaled Nitric Oxide (FeNO) and Biomarkers of Type 2 Inflammation in Adult Patients With Uncontrolled Persistent Asthma Despite Use of Medium-to-High Dose Inhaled Corticosteroids Plus Long-Acting Beta-Agonists (ICS/LABAs)*

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Introduction: Dupilumab, a fully human IL-4R α monoclonal antibody, inhibits interleukins 4 and 13 signaling and showed significant efficacy in a phase 2b asthma trial (NCT01854047). We now report the effects of 24 weeks of dupilumab treatment on FeNO and blood biomarkers.

Methods: Adults (N=776) with uncontrolled persistent asthma for ≥ 12 months (medians: FEV₁ = 62% of predicted; ACQ-5 = 2.6) were randomized to 24 weeks of dupilumab (200 mg or 300 mg every 2 weeks [q2w] or every 4 weeks [q4w]), or placebo subcutaneously, on top of medium-to-high dose ICS+LABA. FeNO and blood biomarkers were measured using commercial assays. Percent changes from baseline were assessed using least-squares (LS) means derived from a mixed-effect model with repeated measures.

Results: LS mean percent changes from baseline to Week 24 for 300 mg q2w/200 mg q2w/placebo, respectively, were: FeNO (-29.4%/-21.9%/+10.9%), serum TARC (-26.7%/-29.4%/+11.0%), plasma eotaxin-3 (-26.6%/-37.8%/+20.0%), and serum total IgE (-46.9%/-52.2%/+11.6%); all $P \leq 0.0001$ versus placebo. Dupilumab suppressed FeNO, TARC and eotaxin-3 with near-maximal decreases by Week 2 which were similar and sustained for the q2w regimens, but smaller for q4w dosing. Serum total IgE gradually declined throughout dupilumab treatment without clear dose-differentiation, while total IgG, IgM and IgA did not decline compared to placebo. The most common adverse event was injection-site reaction (13–26% vs 13% placebo).

Conclusions: The dupilumab q2w dose regimens achieved sustained suppression of type 2 inflammatory biomarkers versus placebo. A specific decline in IgE indicated immunoglobulin switching away from an allergic phenotype in dupilumab treated patients.

Study sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.

OCCURRENCE OF SEVERE ASTHMA EVENTS AND EXACERBATIONS BY LEVEL OF CONTROLLER THERAPY IN PATIENTS WITH ASTHMA IN THE UNITED STATES **

Michael DePietro, MD, Emily Durden, PhD, Kathleen M. Fox, BS, Matthew Brouillette, BS, MPH, Jill R. Davis, MS, Machaon Bonafede, PhD, MPH

RATIONALE: Data on the effect of low controller asthma medication use on mortality and other severe asthma events in the United States is sparse. The study objective was to describe the impact of controller maintenance medication use on the occurrence of severe asthma events and exacerbations.

METHODS: This retrospective claims analysis used the MarketScan[®] Commercial and Medicare Supplemental Databases. Asthma patients aged ≥ 12 years with ≥ 2 short-acting beta-agonist (SABA) claims within a 12-month period between 1/1/2008 – 6/30/2013 and with ≥ 12 months of continuous medical and pharmacy benefits enrollment prior to and following the index SABA claim were included. Patients diagnosed with chronic obstructive pulmonary disease and other respiratory conditions at any time during the study period were excluded. Patients were grouped according to their ratio of controller medications to total asthma medications (asthma medication ratio, AMR) observed during the baseline period (12 months prior to index SABA) as follows: AMR ≤ 0.10 , 0.11 \leq AMR < 0.25 , 0.25 \leq AMR < 0.50 , 0.50 \leq AMR < 0.75 , AMR ≥ 0.75 . The occurrence of severe asthma events, indicated by an asthma-related hospitalization or emergency department (ED) visit; and asthma exacerbation events (defined as an asthma-related hospitalization or ED visit, or a claim for an oral corticosteroid), were evaluated over 12 months. The odds of experiencing severe asthma events and exacerbations were estimated using multivariable logistic regression, adjusted for patient demographic and clinical characteristics.

RESULTS: Included were 168,915 patients treated for asthma; 48.9% had very low/no controller use during the baseline period (AMR ≤ 0.10). SABA use, measured as the average number of canisters per month over 12 months of follow-up, was highest among patients with 0.11 \leq AMR < 0.25 , and declined thereafter with increasing levels of AMR. After multivariate adjustment, the odds of a severe asthma event were 20.2%, 36.5%, and 35.0% lower for patients with 0.25 \leq AMR < 0.50 , 0.50 \leq AMR < 0.75 , and AMR ≥ 0.75 , respectively, versus those in the lowest AMR group (Table 1). A similar pattern of results was observed for asthma exacerbations. In contrast, the odds of a severe asthma event were 90.4% and 113.0% higher for patients with an average monthly SABA use of 1 to < 2 and ≥ 2 canisters per month over 12 months, respectively, versus those with an average monthly use of < 1 canister (Table 1).

CONCLUSION: Very low to no controller asthma medication use and increased SABA use were associated with increased odds of severe asthma events and exacerbations over 12 months. Results may indicate an unmet need among patients with low use of maintenance medications.

Supported by AstraZeneca, LP.

SAFETY AND EFFICACY OF A NOVEL LAMA/LABA CO-SUSPENSION TECHNOLOGY GLYCOPYRROLATE/FORMOTEROL FIXED-DOSE COMBINATION DELIVERED BY MDI: RESULTS OF A ONE-YEAR EXTENSION STUDY IN PATIENTS WITH COPD (PINNACLE-3) **

Nicola A Hanania, Donald Tashkin, Edward Kerwin, James Donohue, Michael Denenberg, Denis O'Donnell, Dean Quinn, Shahid Siddiqui, Chad Oreville, Andrea Maes, Colin Reiser

Rationale: GFF MDI is a novel LAMA/LABA co-suspension technology (glycopyrrolate 18 μ g/formoterol fumarate 9.6 μ g) fixed-dose combination delivered by metered dose inhaler (MDI). Two Phase III randomized, double-blind, placebo-controlled, 24-week studies (PINNACLE-1, PINNACLE-2) supported the efficacy of GFF MDI versus placebo and monocomponents GP MDI (glycopyrrolate 18 μ g) and FF MDI (formoterol fumarate 9.6 μ g MDI), in patients with moderate-to-very-severe COPD. Here we report results from a one-year follow-up from PINNACLE-3, the multi-center, randomized, double-blind, parallel-group, active-controlled safety extension study of PINNACLE-1 and -2.

Methods: Patients with COPD completing 24 weeks' treatment in PINNACLE-1 and -2 received GFF, FF, or GP delivered via co-suspension technology MDI twice-daily or open-label tiotropium 18 μ g dry powder inhaler once-daily for a further 28 weeks of treatment. The primary objective of this one-year extension study was to evaluate the long-term safety of active treatments without a long-term placebo component. The primary efficacy endpoint evaluated the effect of GFF versus its monocomponents on lung function (forced expiratory volume in 1 second [FEV₁]). Secondary endpoints included Self-Administered Computerized Transition Dyspnea Index Focal Score (SAC-TDI), St George's Respiratory Questionnaire (SGRQ), and use of rescue medication over 52 weeks of treatment.

Results: Of 3,274 patients treated with active treatment in PINNACLE-1 and -2, 893 continued the same treatment in PINNACLE-3 (GFF n=290; FF n=213; GP n=219; open-label tiotropium n=171). There were no unexpected safety findings. Across 52-weeks' treatment, the overall incidence of adverse events (AEs) was similar for GFF (64.6%), FF (60.4%), GP (59.9%) and tiotropium (69.2%). The most commonly reported AEs with GFF (nasopharyngitis 6.8%, cough 4.2%, and upper respiratory tract infection 3.8%) were comparable with the monocomponents and with open-label tiotropium. For changes from baseline in trough FEV₁ and peak FEV₁ within 2-hours post-dose across 52-weeks' treatment, GFF demonstrated significant improvement versus FF (65 and 88 mL, respectively), GP (57 and 129 mL, respectively) and tiotropium (25 mL and 93 mL, respectively). GFF also demonstrated significant improvement versus GP ($p < 0.0001$) and open-label tiotropium ($p = 0.0002$) for average daily use of rescue medication, and numerical improvement versus FF ($p = 0.0750$). Numeric trends for improvement with GFF versus individual components were seen for SGRQ. Overall, the results of PINNACLE-3, the 28-week extension study to two Phase III

Conclusions: studies demonstrated long-term safety, tolerability, and consistent and sustained efficacy, of GFF MDI (glycopyrrolate/formoterol 18/9.6 μ g) twice-daily compared with its monocomponents in patients with moderate-to-very-severe COPD over 52 weeks of treatment.

Research Funding Source: This study was supported by Pearl Therapeutics Inc., a member of the AstraZeneca Group.

Drug delivery from a novel LAMA/LABA co-suspension technology of glycopyrrolate/formoterol fixed-dose combination MDI: Evidence of consistency, robustness and patient-use reliability **

Peter Mack, Amber Doty, Jon Schroeder, Kou Vang, Sarvajna Dwivedi

Rationale: To assure consistency of clinical outcomes, orally inhaled products must have consistent *in vitro* delivered dose and aerosolization properties at the time of manufacturing, during storage, and during various scenarios of patient use. Historically, achieving consistency across all of these scenarios has been a significant challenge, particularly for pressurized metered dose inhalers (pMDI), and especially for combination products. Glycopyrrolate/formoterol fumarate (GFF) is a novel long-acting muscarinic antagonist/long-acting β_2 -agonist (LAMA/LABA) co-suspension technology fixed-dose combination delivered by metered dose inhaler (MDI) developed as maintenance bronchodilator treatment for patients with chronic obstructive pulmonary disease (COPD). The novel co-suspension formulation technology¹ suspends the two drugs as microcrystals using spray-dried phospholipid porous particles in hydrofluoroalkane propellant.

Method: *In vitro* drug delivery reproducibility, stability, robustness, and usability of GFF were extensively characterized in parallel with Phase 3 clinical development. Delivered dose uniformity (DDU) was assessed through the labeled number of doses. Aerosol properties (e.g., aerodynamic particle size distribution [aPSD], % fine particle fraction [FPF]) were determined by Next Generation Impactor.

Results: GFF pMDI has reproducible dose delivery and high FPF, for both drugs, very similar to their monotherapy pMDIs. These trends are maintained across various manufacturing batches, and under a wide range of storage conditions, including long-term, accelerated, and temperature cycling conditions. Drug delivery is maintained under simulated patient use scenarios, such as performance after a one meter drop and throughout a patient dosing schedule. Finally, GFF drug delivery performance remains consistent under variations in the patient dosing technique, specifically various pMDI-shaking energies, various delay times between shaking and actuation, and inspiration flow rate ranging from 30-90 liters per minute.

Conclusion: GFF, a pMDI combination of two potent bronchodilator agents, demonstrates consistent drug delivery and aerosolization, regardless of time and condition of testing. This sets a new benchmark for orally inhaled products, and assures confidence in use of MDIs for bronchodilator combination drug delivery.

Research Funding Source: This study was supported by Pearl Therapeutics Inc., a member of the AstraZeneca Group.

THE ICATIBANT OUTCOME SURVEY: MORE THAN 2200 ICATIBANT-TREATED ATTACKS IN PATIENTS WITH TYPE I OR II HEREDITARY ANGIOEDEMA*

Marcus Maurer, Teresa Caballero, Werner Aberer, Andrea Zanichelli, Laurence Bouillet, Vincent Fabien, Hilary Longhurst, for the IOS Study Group.

Background: Icatibant is a bradykinin B2 receptor antagonist used to treat attacks of hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) in adults. The Icatibant Outcome Survey (IOS; NCT01034969) is an international, observational study monitoring the safety and effectiveness of icatibant in a real-world setting. Here we report data from 2245 icatibant-treated attacks in patients with C1-INH-HAE type I or II.

Methods: IOS is conducted at 50 centers in 11 countries. Patient characteristics and icatibant treatment outcomes were recorded at clinic visits. Descriptive retrospective analyses were performed on data collected from July 2009–April 2015.

Results: Icatibant was used to treat 2245 angioedema attacks in 415 patients with type I or II HAE. Mean age at enrollment was 40.7 years (range 16.5–81.2), and 57.8% of patients were female. Proportions of very mild/mild, moderate, and severe/very severe attacks were 7.9%, 31.1%, and 61.0%, respectively (N=1977 attacks). Of attacks with anatomical location data (N=2193), 58.0% affected the abdomen, 41.2% affected the skin, and 7.1% affected the larynx. Most icatibant injections were self-administered (N=1708/2070 attacks; 82.5%). Median time to icatibant administration was 1.5 hours (N=1030 attacks). Median time to symptom resolution was 6.0 hours (N=1025 attacks). Median attack duration was 9.0 hours (N=864 attacks). Icatibant was well tolerated, with no unexpected safety outcomes.

Conclusions: IOS has accumulated a large database of patients with C1-INH-HAE, providing insight into the characteristics of this rare disease. In addition, treatment outcomes of icatibant in the real world were consistent with those from the Phase III studies.

Supported by Shire

Safety of 300IR 5-Grass Pollen Sublingual Tablet for the Treatment of Grass Pollen-Induced Allergic Rhinoconjunctivitis in Adults and Pediatric Subjects with Intermittent Asthma

Gary Steven, MD, Linda Cox, MD, Laura Beveridge, M.Ed, Kathy Abiteboul, PharmD

Introduction: Allergic asthma is frequently associated with grass pollen-induced allergic rhinoconjunctivitis (ARC). Here we present the safety experience across the development program for the 300IR 5-grass pollen sublingual tablet by asthma status.

Methods: Subjects with medically confirmed grass pollen-induced ARC were included in 7 double-blind studies. Those with intermittent asthma not requiring treatment other than inhaled beta-2 agonists (GINA Step 1) could participate. Adverse events (AEs) pooled from the studies were analyzed descriptively. Asthma status was recorded at randomization.

Results: The analysis included 1,878 adults and 312 pediatric subjects. Of these, 328 (17%) adults (300IR=179, Placebo=149) and 66 (21%) pediatrics (300IR=32, Placebo=34) had intermittent asthma at baseline. Percentages of actively-treated subjects reporting drug-related AEs were similar in those with and without asthma (adults: 59% vs. 58%; pediatrics: 53% for both). In both subsets, the respective incidences of AEs leading to discontinuation (mostly application-site reactions) were 6.7% vs. 4.3% (adults) and 3.1% vs. 4.9% (pediatrics). Of the subjects with asthma, 60 adults (300IR 31/179 [17%]; Placebo 29/149 [19%]) and 29 pediatrics (300IR 14/32 [44%]; Placebo 15/34 [44%]) reported an AE of asthma or a related symptom during treatment. Two actively-treated participants (including one pediatric) and 9 who received placebo (including one pediatric) were administered oral corticosteroids as treatment for an AE suggestive of asthma. There were no serious drug-related AEs in any subject with asthma who received 300IR.

Conclusions: Treatment with 5-grass pollen sublingual tablet had a similar safety and tolerability profile in adults and children with and without intermittent asthma.

Supported by Stallergenes Greer

Efficacy and Safety of 300IR 5-Grass Pollen Sublingual Tablet in Polysensitized Subjects with Grass Pollen-Induced Allergic Rhinoconjunctivitis

Linda Cox, MD, Gary Steven, MD, Kevin Renahan, M.Sc., Josiane Cognet-Sice, PharmD.

Introduction: The efficacy and safety profile of 300IR 5-grass pollen sublingual tablet administered daily pre-and co-seasonally has been demonstrated in subjects with grass pollen-induced allergic rhinoconjunctivitis (ARC). Using data from 7 clinical trials (one pediatric) of the development program, we present the results in 1,388 polysensitized subjects.

Methods: At enrollment, subjects with medically confirmed grass pollen-induced ARC underwent skin testing to 5-grass mix or timothy and a panel of geographically relevant aeroallergens. Those testing positive to 5-grass/timothy and at least one other allergen were considered polysensitized. The Combined Score (scale 0-3) equally weighing symptom and rescue medication scores was analyzed (ANCOVA) for the single or first pollen period of 4 studies. Adverse events (AEs) pooled from all studies were analyzed descriptively.

Results: 1,201 (64%) of 1,878 adults (300IR=663, placebo=538) and 187 (60%) of 312 pediatric subjects (300IR=92, placebo=95) were polysensitized. Significant differences from placebo in the mean Combined Score were observed in both actively-treated adult (-0.14, relative difference: -26.2%) and pediatric (-0.24, relative difference: -36.3%) subsets. As per overall population, application-site reactions such as oral pruritus (adults: 24.9%, pediatrics: 19.6%), throat irritation (adults: 20.8%, pediatrics: 13.0%) and mouth edema (adults: 9.0%, pediatrics: 9.8%) were the most commonly reported AEs. Three serious drug-related AEs occurred in actively-treated adults: hypersensitivity (one polysensitized subject), angioedema and diarrhea (two monosensitized subjects) and resolved.

Conclusions: 300IR 5-grass pollen sublingual tablet was effective in subjects with multiple sensitizations, whether adults or children. The safety profile in both polysensitized subpopulations was consistent with that of overall population.

Sponsored by Stallergenes Greer

Dupilumab Improves Patient-Reported Outcomes in Uncontrolled Persistent Asthma: Results from a Phase 2b Clinical Trial

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Introduction: Uncontrolled persistent asthma is associated with substantial disease burden, impacting patient quality of life (QoL). In a phase 2b clinical trial (NCT01854047), dupilumab (a fully human anti-interleukin [IL]-4 receptor- α monoclonal antibody that inhibits IL-4 and IL-13 signaling) improved lung function and reduced severe exacerbation rates. Patient reported outcomes (PROs) from this trial are presented.

Methods: 776 adults with uncontrolled persistent asthma while on medium-to-high dose inhaled corticosteroids plus a long-acting beta-agonist (ICS/LABA) were randomly allocated to 24 weeks of add-on therapy with dupilumab 200 mg or 300 mg every 2 weeks (q2w), every 4 weeks, or placebo (q2w results are presented). PROs included 5-item Asthma Control Questionnaire (ACQ-5), morning (AM) and evening (PM) asthma symptom scores, Sino-Nasal Outcome Test (SNOT-22), and Asthma Quality of Life Questionnaire (AQLQ).

Results: At baseline, demographics, clinical characteristics, and PRO scores were similar across groups. At Week 24, both dupilumab q2w doses significantly improved on ACQ-5, AM and PM scores, AQLQ (all $P \leq 0.01$), and several AQLQ domains ($P \leq 0.05$). Dupilumab 300 mg q2w significantly reduced sino-nasal symptoms (SNOT-22, $P \leq 0.001$). Responder rates, based on minimum clinically important differences, were significantly greater for both dupilumab groups vs placebo for AM and PM scores; dupilumab 200 mg (ACQ-5) and 300 mg (SNOT-22) also achieved significantly greater responses (all $P \leq 0.05$). Most common adverse events were upper respiratory tract infection and injection-site erythema.

Conclusions: In adults with uncontrolled persistent asthma, dupilumab as add-on to ICS/LABA significantly improved symptom and QoL-related PROs vs placebo. Dupilumab had an acceptable safety profile.

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Persistent Treatment Effect with Grass Synthetic Peptide Immuno-Regulatory Epitopes on Grass Allergy Symptoms in the Environmental Exposure Unit after a Third Season of Natural Exposure

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Background: Grass Synthetic Peptide Immuno-Regulatory Epitopes (Grass-SPIRE) has previously been shown to reduce rhinoconjunctivitis symptoms in subjects with grass pollen allergy following a short course of treatment over 14 weeks and subsequent exposure to two natural grass pollen seasons. In the current study, persistence of the treatment effect after a third grass pollen season was evaluated.

Methods: This was a follow-up study to a multicentre, randomised, double-blind, placebo-controlled, parallel group study. Subjects who completed the original study in 2012 and had a mean Total Rhinoconjunctivitis Symptom Score (TRSS) of ≥ 8 at Baseline could be enrolled (safety population, N=85). Environmental Exposure Unit (EEU) visits, in which subjects underwent 3-hour exposure to rye grass allergen on 4 consecutive days, were scheduled after a third grass pollen season, approximately 2 years after the original post-treatment challenge. Assessments included TRSS, nasal and non-nasal symptom scores. There was no further treatment with Grass-SPIRE.

Results: 84 subjects were included in the full efficacy analysis. For the primary efficacy endpoint (Days 2, 3 and 4, 1-3 hour assessments), mean changes in TRSS of -6.2 ($p=0.113$ versus placebo) and -6.4 ($p=0.076$ versus placebo) were found in subjects treated with 8 x 6 nmol and 4 x 12 nmol Grass-SPIRE, respectively. These reductions in TRSS were greater than those in the 8 x 12 nmol Grass-SPIRE group. Responder analysis revealed that most subjects given 8 x 6 nmol and 4 x 12 nmol Grass-SPIRE had a clinically relevant response to treatment. Among the 73 subjects who had also completed a follow-up evaluation after 2 seasons, the treatment effect was apparent at all three evaluations for the 8 x 6 nmol (LS mean difference in TRSS in season 1; -2.9, $p=0.075$, season 2; -5.0, $p=0.004$ and season 3; -3.4, $p=0.033$) and 4 x 12 nmol doses (season 1; -4.0, $p=0.016$, season 2; -4.5, $p=0.008$ and season 3; -4.1, $p=0.010$).

Conclusions: The effect of Grass-SPIRE treatment persisted after three grass pollen seasons despite no further doses being administered, with continued efficacy being demonstrated for both the 8 x 6 nmol and 4 x 12 nmol doses. Subjects who participated in all three evaluations demonstrated a robust and persistent effect with both doses across all three seasons.

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