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A Case of Hereditary Angioedema Presenting with Ileocolic Intussusception

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Objectives: To present a rare case of intussusception in an adult with hereditary angioedema (HAE).

Case Presentation: A 38-year-old female with a past medical history of type 2 HAE presents with seven days of progressive right lower quadrant abdominal pain and distension, nausea, constipation, and decreased oral intake. Unlike her previous HAE episodes, her symptoms persisted despite two 30 mg subcutaneous injections of icatibant. At presentation, she was afebrile, normotensive, and non-tachycardic. Bowel sounds were diminished in all four abdominal quadrants with tenderness to light palpation. She had a palpable mass in the right lower quadrant. Otherwise, the physical examination was normal.

Results: Laboratory findings revealed a C4 level of 3.4 (normal 15 - 57 mg/dL), consistent with HAE. The abdominal ultrasound and computed tomography scan revealed diffuse bowel wall thickening and intussusception of the ascending colon. She was started on intravenous (IV) Berinert, a C1 esterase inhibitor, 20 units/kg every 48 hours. An exploratory laparotomy revealed a non-reducible ileocolic intussusception with gross findings of tissue necrosis. A hemicolectomy was performed without complication or need for ostomy. She was discharged home with icatibant on-demand therapy with plans to initiate IV HAE prophylactic therapy with Cinryze, another C1 esterase inhibitor, 1000 units three times weekly.

Conclusions: HAE is characterized by bradykinin mediated angioedema. Lethal laryngeal angioedema has been reported. HAE commonly presents with recurrent abdominal crampy pain associated with diffuse intestinal angioedema leading to unnecessary exploratory laparotomies. Only a few cases of HAE associated intussusception are reported in the medical literature and most occur in childhood or adolescence. This case is unique in that the HAE episode along with concurrent intussusception occurred in her late 30's.

Chronic Eosinophilic Pneumonia in an Uncontrolled Asthmatic

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Objectives: Recognize idiopathic chronic eosinophilic pneumonia (ICEP) in a febrile patient who presents like an asthma exacerbation with peripheral eosinophilia.

Method: Retrospective chart review of a 35-year-old male with a history of uncontrolled asthma who presented with three months of worsening cough, wheezing, and shortness of breath despite Budesonide/Formeterol inhaler use. On the day of admission, he developed new onset fevers, which prompted him to go to the hospital. Social history was significant for hookah, but not cigarette smoking.

Results: The differential on a peripheral CBC revealed 16.3% eosinophils. ANCA, ANA, stool ova and parasites, Aspergillus IGE antibody, and Aspergillus antigen were negative. While chest radiograph was unrevealing, continued fever prompted a computerized tomograph scan of the chest, which demonstrated upper lobe predominant, patchy, peripheral, ground-glass opacities and consolidations. Bronchoscopy with bronchoalveolar lavage (BAL) was pursued due to concern for ICEP, which revealed 36% eosinophils. A diagnosis of ICEP was made and the patient was treated with steroids, with improvement in symptoms.

Conclusion: Diagnosis of ICEP is made in patients with febrile illness, upper lobe predominant, peripheral, opacities on chest imaging, and BAL eosinophilia. In those with an asthma exacerbation and fevers, consider ICEP in the differential by looking for peripheral eosinophilia and characteristic infiltrates on chest imaging.

Use of Trigger Point Injections in Treating Sinus Headache in an Allergy Clinic

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Objective: To investigate the connection between the relief of sinus headache and TPI.

Method: Questionnaires were completed by 22 adult allergy clinic patients with varying levels of head and sinus pain undergoing lidocaine based trigger point injection. Measures included using a 0-10 Numeric Pain Rating Scale, time to relief onset, symptom relief and duration, and tolerability of procedure.

Results: The median patient age was 45 years (range 28-68), with 54% of patients rating the quality of head pain as 8 or greater and 59% of patients reporting sinus pain as 7 or higher prior to treatment. 91% of patients also reported that this pain affected them 2-6 days per week. Post-treatment, 91% of patients reported head pain and sinus pain reduced to a 3 or less. In addition, 100% survey participants described the procedure as "very tolerable" or "tolerable."

Conclusion: Lidocaine needling of myofascial trigger points appears to be an effective treatment for both head and sinus pain. Patients reported that trigger point injections were tolerable and lowered their overall pain level. Further study is necessary to understand sinus inflammation and to determine the relationship between TPI and sinus headache.

Urticaria and Angioedema following three retinal injections: What is the culprit?

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Introduction: A 79-year-old female with macular degeneration was referred to the Allergy/Immunology clinic from ophthalmology for the evaluation of a potential allergy to anti-vascular endothelial growth factor (VEGF) treatments for macular degeneration. The patient developed urticaria and angioedema immediately following three separate retinal injections of aflibercept, ranibizumab, and bevacizumab. Injections of anti-VEGF treatments were discontinued with subsequent progression of the patient's macular degeneration.

Methods: Procedure and medication records were obtained and reviewed for each retinal injection. All medications used in each procedure, including the anti-VEGF therapy (aflibercept, ranibizumab, bevacizumab), topical anesthetics (tetracaine, proparacaine hydrochloride) and antiseptic (povidone) were evaluated via skin prick test and intradermal testing. A test dose challenge was completed for aflibercept, ranibizumab, and bevacizumab.

Results: Skin prick and intradermal testing with appropriate controls were negative to aflibercept, ranibizumab, bevacizumab, and povidone. Intradermal testing was positive to tetracaine and proparacaine hydrochloride. The patient passed test dose challenges to aflibercept, ranibizumab, and bevacizumab. Due to her positive hypersensitivity testing to two ester anesthetics, the patient underwent skin prick and intradermal testing to the amide anesthetic, lidocaine. This was negative and the patient tolerated a subsequent graded challenge to lidocaine. Based on her allergy evaluation, the patient was deemed to have an IgE-mediated hypersensitivity to ester local anesthetics. She successfully resumed anti-VEGF therapy with an amide local anesthetic for her macular degeneration.

Conclusions: This case highlights the importance of a thorough allergy evaluation of all medications used during ophthalmic procedures to determine the causative agent of a reaction.

Red Touches Yellow Can Kill a Fellow, but the Horse Almost Killed Jack

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Introduction: Serum sickness (SS) from coral snake antivenom.

Methods: A 64-year-old male with no relevant medical history presents to the hospital after a coral snake bite on the right index finger. He is treated with *Micrurus* North America immune F(ab')₂ equine antivenom (research trial) and is discharged. Two days later, he experiences bilateral calf pain, malaise, ecchymosis at the bite site, wrist stiffness and a generalized maculopapular rash on his anterior thighs, upper extremities and lower abdomen. Vital signs and laboratory results (including UA) are normal. His condition improves with loratadine 10 mg daily, famotidine 20 mg twice daily, and triamcinolone 0.1% ointment twice daily.

Results: Coral snakes (genus *Micrurus*, two species in North America) live in the southern United States. Their neurotoxin venom affects the neuromuscular junction pre- and post-synaptic clefts. The coral snake bite effects are dose-dependent and range from local pain and swelling to dysphonia and respiratory failure. Death is rare. Antivenom is produced in horses following immunization with venoms from *Micrurus* species and derived from horse plasma.

SS, which causes fever, arthralgias and a pruritic maculopapular rash, usually occurs within 5-14 days after horse antivenom. Depending on the antivenom characteristics, the incidence can range from 40-80%. The immunologic mechanism is secondary to host IgG antibody production against equine antivenom resulting in immune complex formation and complement activation. Treatment includes glucocorticoids and non-steroidal anti-inflammatory and H1 and H2 antihistamine medications.

Conclusion: This is a case report of SS secondary to horse-derived coral snake antivenom.

Eval Common Variable Immunodeficiency Presenting With Recurrent Ascending Cholangitis

John A. Johnson, MD, Tina Abraham, MD, Monica Sanhdu, MD, Haig Tcheurekdjian, MD, Robert Hostoffer, MD

Introduction: Common variable immunodeficiency (CVID) is the most common, symptomatic primary immunodeficiency affecting 1 in 50,000. Its diagnosis is based on a history of recurrent upper and lower respiratory tract infections as well as a diminished to absent quantitative and qualitative serum immunoglobulin levels. We describe a case of a 61-year-old female who presented with recurrent ascending cholangitis every other week for 8 years as the primary manifestation of CVID.

Methods: Quantitative serum immunoglobulin isotypes as well as pneumococcal titers before and after the administration of the polysaccharide and conjugate pneumococcal vaccinations. Ascending cholangitis was diagnosed clinically based on fever and right upper quadrant abdominal pain along with radiographic imaging studies supportive of the diagnosis.

Results: Both IgA and IgG were abnormally low at 58 mg/dL (range, 70 to 400 mg/dL) and 571 mg/dL (range, 700 to 1600 mg/dL), respectively. Both the polysaccharide and conjugate pneumococcal vaccinations did not elicit an adequate serologic response. Alkaline phosphatase was 216 U/L (range, 46 to 111 U/L) and alanine aminotransferase was 82 U/L (range, 7 to 54 U/L). Radiographic imaging studies, including MRI, of the abdomen revealed pneumobilia.

Conclusion: This is the first case of CVID to present with recurrent ascending cholangitis. Clinicians must be able to recognize the global pattern of recurrent infections that allude to CVID. The prompt diagnosis and treatment of CVID are essential in order to screen for associated conditions that contribute to the morbidity and mortality of untreated CVID.

Green Tea-Induced Anaphylaxis

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Introduction: Tea is one of the oldest produced beverages and has been consumed since 2700 B.C. Anaphylaxis caused by tea produced from the *Compositae* family has been reported in the literature, but no cases of anaphylaxis from green tea, which is produced from *Camellia sinensis*, have been reported. We describe the first case of green tea-induced anaphylaxis in a patient with a convincing history and supportive physical findings.

Methods: Skin prick testing (SPT) with caffeine and with green tea was completed. A Celestial brand, green tea pod was used for the preparation for the green tea SPT. Specific IgE to tea was obtained.

Results: SPT with green tea elicited a 6mm wheal with a 61mm flare. The same green tea SPT preparation was non-reactive for five volunteers with no known food allergies. SPT for caffeine was non-reactive. Specific IgE for tea was negative.

Conclusion: Anaphylaxis induced by tea produced from the *Compositae* family has been reported, however, no cases of anaphylaxis from green tea, which is produced from *Camellia sinensis*, have previously been reported. The demand for green tea is growing among consumers with its production expected to increase to 2.97 million tons a year by 2023. Now that green tea-induced anaphylaxis has been established, clinicians must be aware of its potential role in food hypersensitivities. This is the first case of green tea-induced anaphylaxis.

Increased risk of Ace-Induced angioedema following thrombolysis in acute stroke

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Introduction: Angiotensin-converting enzyme (ACE) inhibitors are the most common cause of drug-induced angioedema in United States. They are used in hypertension, coronary artery disease, diabetes and kidney disease. This population is also at higher risk of acute ischemic strokes, for which recombinant tissue plasminogen activator (rtPA) represents the standard of care. We present a case of Ace-inhibitor associated angioedema after tPA administration in a patient successfully treated with icatibant.

Methods: Case report.

Results: A 51-year-old female with hypertension, diabetes and end stage kidney disease was admitted to the hospital for management of right basal ganglia bleed. Neurological status worsened and she was intubated for airway protection and treated with (rtPA). She developed oropharyngeal angioedema six hours after rtPA infusion. Review of previous medications revealed use of Lisinopril. Physical exam was negative for any other skin findings. C4 was normal. Brain MRI preceding thrombolysis showed mild tongue swelling and soft tissue edema which worsen the next days. CT scan of the neck confirmed swelling and no evidence of trauma. Treatment with icatibant was recommend. Patient experienced marked improvement and was successfully extubated.

Conclusion: The mechanism behind angioedema after alteplase treatment and ACE-inhibitors has been thought to be related to activation of the complement and kinin cascade. ACE-inhibitors prolong bradykinin half-life due to absence of plasma kininases.

Awareness about the increased risk for Ace-induced angioedema in patients treated with alteplase should be increased. Treatment with antagonist of bradykinin B2 receptors represents an alternative targeting the mechanism.

Video-based training on proper EpiPen(Jr) administration and food allergy knowledge among Chinese, Spanish, and English populations in Boston.

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Background: Eight percent of children in the United States have food allergies. Of these, 38.7% have a history of severe reaction(s) necessitating the use of an EpiPen(Jr). Studies indicate that early administration of epinephrine is attributed to significant reductions in reaction severity. Delays in epinephrine injection result from both incorrect use and lack of knowledge regarding the anaphylactic reaction.

Objective: To examine the effectiveness of an educational video [describing food allergy and use of EpiPen(Jr) for management of anaphylaxis] provided to caregivers of children with food allergy.

Method: We developed video-based education regarding food allergy and proper administer of EpiPen(Jr) in English, Spanish, and Chinese. Participant knowledge was tested prior to and following the video using a validated questionnaire. Proper use of the EpiPen was evaluated via demonstration.

Results: Analysis included 45 participants (34% white, 22% black, 20% Asian, 24% Hispanic). At baseline, mean score of the knowledge test was 9.6/18; this increased to 14/18 following the video (68%, $p < 0.00001$). Similarly, the EpiPen(Jr) assessment increased from a mean score of 3.5 to the maximum of 6 (58%, $p < 0.00001$). Perception of worth was assessed using the 6-point Likert scale, with all categories scoring above the favorable mean.

Conclusions: Video-based education is a valuable and cost-effective method of improving food allergy knowledge and EpiPen(Jr) compliance in English, Chinese, and Spanish speaking populations.

Silent Airflow Obstruction and Air Trapping in Children Admitted to the Hospital with Asthma

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Rationale: Lung function tests are often underutilized in assessing children hospitalized with asthma prior to discharge. We hypothesized that children with status asthmaticus may have more airflow obstruction and air trapping on lung functions than is apparent by physical examination alone.

Methods: We retrospectively reviewed pulmonary function tests (airflow and lung volumes) of children admitted to Norton's Children's Hospital (a tertiary care center) with asthma. Patients performed pulmonary function testing (according to ATS criteria) when the treating physician felt the patient was ready for discharge based on clinical improvement. Patients (ages 6-17, mean 12 years) were included if they had an admitting diagnosis of asthma and were able to perform lung functions (both spirometry pre and post bronchodilator and lung volumes). Lung functions were excluded if they showed poor to variable effort based on flow-volume loop or a purely restrictive pattern in airflows.

Results: We reviewed one hundred sixty-three lung function tests over a two year period. The mean FEV₁/FVC ratio measured 78 (range 46 to 100), while the mean RV/TLC ratio measured 32 (range 14-53). The lung functions showed moderate to severe air trapping (RV/TLC >31) in 55% tests. 44% of tests had FEV₁ less than 80 percent predicted. 58% of tests showed FEV₁/FVC ratio less than or equal to 0.8. We observed no correlation between the FEV₁/FVC and RV/TLC ratios. The highest RV/TLC ratio (53) had a normal FEV₁/FVC ratio (91).

Conclusions: We found children admitted with asthma to have more severe airflow obstruction and air trapping on spirometry than was apparent on physical assessment.

Assessing an intervention to improve influenza immunization rate in asthmatic patients on Biologics

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Objective: It is recommended that all asthmatics receive a yearly influenza vaccine, but many asthmatics (including those with severe disease) do not received the vaccine. We sought to assess whether offering influenza vaccine to asthmatic patients at the time of their monthly biologic therapy for asthma increases their chances of getting the vaccine.

Method: Thirty-three asthmatic patients were offered influenza vaccine at the nurse visit for their monthly Omalizumab and Mepolizumab therapy. These patients were also asked if they received influenza vaccine last year. The study was done over period of 3 months from october to december 2016.

Results: For the year 2016, 28/33 (84%) patients received their vaccine compared to 25/33 (76%) who received it last year. The additional three patients who received the vaccine did not receive it at our clinic ($p=0.537$). All of the patients who refused the vaccine this year had also refused the vaccine last year. Reasons for refusal were history of egg allergy, fear of adverse effects, and personal beliefs.

Conclusion: Offering influenza vaccine to asthmatic patients at the time they are getting their monthly asthma biologic therapy did not increase their probability of getting the vaccine. We need a different strategy, possibly including more patient education about the safety and importance of influenza vaccine, to ensure that all asthmatics are immunized.

Worsening Asthma in a Patient with a History of Sarcoidosis

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Introduction: The purpose of this study is to describe asthma exacerbation and atopy in a patient with a sarcoid history and if both diseases can coexist.

Case Presentation: A 43-year-old African-American female was evaluated in January 2016 complaining of chronic cough and wheezing for uncontrolled asthma and atopy. She has asthma, COPD, hypertension and a sarcoid history, previously diagnosed based on age, sex, ethnicity and presentation. No confirmatory biopsy was done. She has strong family history of sarcoidosis but denies any familial atopic diseases. She was a former smoker with a 15-pack-year. On physical examination, vital signs were stable. She had boggy nasal turbinates and wheezing in bilateral lung fields. Serum IgE was elevated 2251 kU/L; sIgE was positive for common ragweed, *Dermatophagoides*, maple, oak, peanut, banana, giant ragweed, mugwort, *Penicillium notatum*, *Cladosporium herbarum*, *Hevea brasiliensis*, grass, and dog dander. Chest X-ray showed streaky nodular reticular markings on bilateral lungs with chronic interstitial lung disease. PFT showed mixed obstructive and restrictive pattern with reduced diffusion lung capacity. She was prescribed oral steroids, ipratropium, budesonide/formoterol, and albuterol inhalers.

Discussion: Poorly controlled asthma and exacerbations can occur in a patient with a history of sarcoidosis. Possible sarcoid etiologies are infection and environmental agents. She has a strong family history of sarcoidosis. Exposure to molds has been associated with an increased disease risk. The presence of sarcoidosis could lead to deterioration of asthma control.

Conclusion: A sarcoid history can potentially lead to worsening asthma.

Symptomatic Burden of Asthma Patients Adherent to Medium- or High-Dosage ICS/LABA: Findings from a US Real World Survey

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Rationale: Asthma control is typically achieved through treatment adherence and intensification, including upward titration of inhaled corticosteroids (ICS). However, not all patients reach adequate asthma control with such interventions. This study describes the symptom burden of asthma patients adherent to medium- or high-dosage ICS/long-acting beta2-agonist (LABA) treatment.

Methods: Cross-sectional data from 3 US Adelphi asthma surveys, conducted during 2013-2016, were analysed in diagnosed asthma patients, prescribed medium- or high-dosage ICS/LABA treatment with self-reported medium to high adherence (Morisky Medication Adherence Scale). 629 physicians completed patient record forms for 5 asthma patients each, recording clinical information. These patients were invited to complete a questionnaire, including the Asthma Control Test (ACT). Descriptive statistics were reported.

Results: 428 patients (mean age 44 years; 62% female; 2.4% smokers) met inclusion criteria. Mean pre-bronchodilator FEV₁ was 65.2% predicted normal. 31% (130/419) of patients reported experiencing symptoms more than twice a week during the latest 4 weeks. Most troublesome symptoms were shortness of breath (34.4% [89/259]) and wheezing (24.7% [64/259]). Mean symptom-free days during the latest 30 days was 17.8. Asthma was reported to impact leisure or personal time frequently or constantly by 11.1% (46/414) of patients. 50.6% (204/403) and 14.6% (59/403) of patients had ACT scores of ≤ 19 (not well-controlled) and ≤ 14 (poorly-controlled), respectively.

Conclusions: Findings across several measures suggest asthma control may not be achieved in a considerable percentage of patients adherent to medium- or high-dosage ICS/LABA treatment. Research is needed to identify novel treatment strategies for patients not responding to medium- to high-dosage ICS/LABA treatment.

Supported by: AstraZeneca

Treatment modification and costs in patients with chronic obstructive pulmonary disease initiating long-acting bronchodilator monotherapy

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Introduction: Patients with chronic obstructive pulmonary disease (COPD) often are treated with a long-acting bronchodilator alone or in combination with other controllers. This study investigated the effects of long-acting bronchodilator monotherapy on treatment patterns and healthcare utilization and costs in patients with COPD.

Methods: COPD patients ≥ 40 years old initiating monotherapy with either a long-acting beta-agonist (LABA) or anticholinergic (LAMA) (index date = first prescription date) between 1/1/2008 and 1/31/2015 were identified from a large US claims database. COPD was defined based on the presence of ICD-9 codes on ≥ 2 separate medical claims on different service dates. Patients had ≥ 1 year of continuous enrollment pre- and post-index date. Patients with inhaled corticosteroid (ICS), LABA, or LAMA use in the year prior to the index date and those with cystic fibrosis were excluded. Treatment augmentation was defined as intensification to dual (i.e., ICS/LABA, LABA/LAMA, or ICS & LAMA) or triple (i.e., ICS/LABA + LAMA) therapy, based on pharmacy fills on the date of first augmentation. Patients were followed until the earliest of treatment augmentation, discontinuation of long-acting bronchodilator therapy (≥ 60 -day gap), health plan disenrollment, death, or the study end (1/31/2016). Per patient per month (PPPM) all-cause and COPD-related healthcare utilization and costs were ascertained in the post-index period.

Results: The study population included 27,394 COPD patients (mean age: 68.4, women: 49.9%) initiating long-acting bronchodilator monotherapy. Among these patients, 18.2% had treatment augmentation, 7.6% continued on long-acting bronchodilator monotherapy until the end of follow up, and 74.2% discontinued long-acting bronchodilator monotherapy, during a mean follow-up duration of 192.7 \pm 308.0 days. For patients with treatment augmentation, the mean time from long-acting bronchodilator monotherapy initiation to therapy augmentation was 177.7 \pm 282.3 days, with 75.5% augmenting to triple therapy. A total of 16.1% of patients had a COPD-related emergency department (ED) visit or inpatient (IP) admission while on long-acting bronchodilator monotherapy post-index. COPD-related and all-cause mean costs PPPM while on monotherapy post-index were \$1,205.53 \pm \$4,063.09 and \$2,402.11 \pm \$5,499.29, respectively.

Conclusions: Among COPD patients initiating long-acting bronchodilator monotherapy, only 7.6% remained on monotherapy, while 74.2% discontinued and 18.2% augmented treatment during follow-up. COPD-related costs were 50% of all-cause costs. There was continued resource use representing half of patients' health care costs suggesting continuing COPD symptoms. More information is needed regarding the factors leading to the significant proportion of patients needing therapy augmentation or discontinuing monotherapy.

Supported by: AstraZeneca, LP.

Functionality, Reliability, and Performance of an Accessorized Pre-Filled Syringe With Home-administered Subcutaneous Benralizumab for Adult Patients With Severe Asthma

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Introduction: Benralizumab, an anti-eosinophil monoclonal antibody, is in development as an add-on treatment for severe, uncontrolled, eosinophilic asthma. During Phase III trials, 1,2 benralizumab significantly reduced annual asthma exacerbation rates and was well-tolerated. The GREGALE study (NCT02417961) assessed patient- and caregiver-reported functionality, performance, and reliability of an accessorized pre-filled syringe (APFS) used to administer benralizumab subcutaneously in an at-home setting.

Methods: In this multicenter, open-label study, 116 patients with severe asthma (i.e., uncontrolled despite receiving medium- or high-dosage inhaled corticosteroids, long-acting β_2 -agonists, and oral corticosteroids with or without additional asthma controllers) received up to five APFS-administered subcutaneous doses (Weeks 0, 4, 8, 12, and 16) of 30-mg benralizumab. Patients and caregivers were trained during administration of the first three doses at the study sites. The last two doses were home-administered by the patient/caregiver. Primary endpoints were percentage of patients/caregivers who successfully administered benralizumab at home, percentage of APFS returned to study sites and evaluated as functional, and percentage of APFS returned as malfunctioning to Product Complaints. Secondary endpoints assessed efficacy (Asthma Control Questionnaire-6 [ACQ-6]), safety, and peripheral blood eosinophil count.

Results: Nearly all patients and caregivers successfully administered benralizumab with an APFS at home (Week 12: 112/114, 98%; Week 16: 108/109, 99%). Two at-home administrations were unsuccessful because of patient-use error. One APFS was recorded as nonfunctional because it was not returned for evaluation. Product Complaints identified only 1 APFS malfunction of 573 dispensed. Mean ACQ-6 scores decreased from baseline (BL) through all post-BL time points through end of treatment (BL: mean 2.14 [standard deviation {SD} 0.81]; Week 20: mean 1.40 [SD 0.90]). Near-complete depletion of eosinophils was observed at end of treatment vs. BL (BL: median 250 cells/ μ L [interquartile range {IQR}] 175–430 cells/ μ L]; and Week 20: median 0 cells/ μ L [IQR 0–10 cells/ μ L]). Incidences of serious adverse events and adverse events leading to benralizumab discontinuation were 6.0% and 2.6%, respectively. Most common adverse events ($\geq 5\%$ of patients) were nasopharyngitis, upper respiratory tract infection, headache, and sinusitis. Five patients (4.3%) experienced injection-site reactions, including injection-site hemorrhage (n=2), erythema, induration, and pain (n=1 each).

Conclusions: Most patients and caregivers successfully administered benralizumab in an at-home setting. The APFS was functional, reliable, and performed well.

Supported by: AstraZeneca

Effect of Glycopyrrolate/Formoterol Fumarate Fixed-Dose Combination Metered Dose Inhaler (GFF MDI) Delivered by Novel Co-Suspension™ Delivery Technology on Daily Symptoms in Patients with COPD

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Introduction: As patients with chronic obstructive pulmonary disease (COPD) are affected by daytime and night-time symptoms, 24-hour symptom control is important. This post-hoc analysis of pooled data from two Phase III studies assessed the effect of glycopyrrolate/formoterol fumarate metered dose inhaler (GFF MDI) compared to monocomponent (glycopyrrolate [GP] and formoterol fumarate [FF]) and placebo MDIs on daily, daytime, and night-time symptom scores, and the influence of baseline symptom burden on these endpoints.

Methods: PINNACLE-1 and -2 (NCT01854645 and NCT01854658, respectively) were multicenter randomized, double-blind studies in patients with moderate-to-very severe COPD. Patients received GFF 18/9.6 μ g (equivalent to glycopyrronium/formoterol fumarate dihydrate 14.4/10 μ g), GP MDI 18 μ g, FF MDI 9.6 μ g, or placebo MDI (7:6:6:3), twice daily for 24 weeks. Patients recorded daily daytime and night-time clinical symptoms (cough, shortness of breath, sputum volume, and rescue Ventolin HFA use) in an eDiary. Patients' responses to diary questions were assigned numeric symptom scores, the sum of which formed the total symptom score. Results were stratified according to baseline symptom burden based on COPD assessment test (CAT) score.

Results: In the pooled intent-to-treat population (n=3699); 45.2% of patients were ≥ 65 years old and 55.9% were male. Baseline CAT scores were < 10 in 12%, ≥ 10 in 87%, ≥ 15 in 69%, and ≥ 20 in 44% of patients (baseline CAT data were missing for 17 patients [$< 1\%$]). GFF MDI improved the least squares mean change from baseline over 24 weeks in total symptom scores versus GP, FF, and placebo MDIs. Benefits versus FF and placebo MDIs were greater for patients with higher baseline CAT scores, and largest for patients with baseline CAT scores ≥ 20 . Such a relationship was not observed for the comparison to GP MDI. Improvements in total symptom scores were mostly driven by improvements in shortness of breath and rescue medication use, but benefits versus placebo were also observed for sputum volume and night-time awakenings. Benefits in daytime and night-time symptoms were observed.

Conclusion: GFF MDI showed improvements throughout 24 hours in eDiary-reported symptoms versus placebo and monocomponent MDIs. In general, the extent of the improvements in symptom scores increased with increasing baseline CAT score. Therefore, following treatment with GFF MDI, patients with a greater baseline symptom burden may experience a larger improvement in daily symptoms than patients with a lower baseline symptom burden.

Supported by: AstraZeneca

LAMA/LABA Glycopyrrolate/Formoterol Fixed-Dose Combination, Delivered Using a Novel MDI Co-Suspension™ Delivery Technology Reduces Risk of Clinically Important Deteriorations in COPD Versus Placebo and Monocomponent MDIs

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Rationale: It is important to understand whether treatments can prevent disease deterioration in patients with chronic obstructive pulmonary disease (COPD). Clinically important deterioration (CID) is an exploratory composite endpoint that examines the effects of therapeutic approaches on COPD outcome. Glycopyrrolate/formoterol fumarate (GFF) is a novel, long-acting muscarinic antagonist/long-acting β_2 -agonist (LAMA/LABA) fixed-dose combination delivered by metered dose inhaler (MDI) using Co-Suspension™ Delivery Technology. This analysis compared the effects of GFF MDI 18/9.6 μg (equivalent to glycopyrronium/formoterol fumarate dihydrate 14.4/10 μg) versus placebo MDI and monocomponents (GP MDI 18 μg and FF MDI 9.6 μg) on the risk of CID of COPD.

Methods: Data from two Phase III randomized, double-blind, placebo-controlled, parallel-group, multicenter studies (PINNACLE-1 and -2 [NCT01854645; NCT01854658]) were pooled for this post-hoc analysis. In each study, patients with moderate-to-very severe COPD received 24 weeks' treatment with GFF MDI, GP MDI, FF MDI, or placebo MDI twice daily (7:6:6:3). CID was defined as a ≥ 100 mL decrease from baseline in trough forced expiratory volume in 1 second (FEV₁); or a ≥ 4 unit increase in St George's Respiratory Questionnaire (SGRQ) total score; or the occurrence of a moderate/severe COPD exacerbation. A 'sustained' CID was a FEV₁ or SGRQ event observed on two consecutive visits or on $\geq 50\%$ of the subsequent visits, or the incidence of any moderate/severe exacerbation.

Results: The pooled intent-to-treat population included 3249 patients who were treated with GFF MDI (n=1035), GP MDI (n=889), FF MDI (n=884), or placebo MDI (n=441). GFF MDI decreased the risk of patients experiencing a first CID or sustained CID compared with placebo MDI, with a time-to-event hazard ratio (HR) (95% confidence interval [CI]) of 0.56 (0.49, 0.64) and 0.52 (0.44, 0.61), respectively. Similar results were observed for GFF MDI versus GP and FF MDIs (HR [95% CI] for time to first CID 0.76 [0.68, 0.85] and 0.83 [0.74, 0.93], respectively). Furthermore, 39% of patients who received GFF MDI remained CID-free over 24 weeks, versus 26%, 31%, and 36% of patients with placebo, GP, and FF MDIs, respectively.

Conclusion: GFF MDI decreased the risk of patients experiencing a first CID or sustained CID compared with placebo and monocomponent MDIs. This finding suggests broader benefits of GFF MDI on airway stability and prevention of disease deterioration for patients with COPD.

Supported by: AstraZeneca

Psoriasisif Benralizumab Significantly Reduced Oral Corticosteroid Dosages and Asthma Exacerbation Rates for Patients With Severe, Uncontrolled Asthma: Results of the ZONDA Phase III Trial

Parameswaran Nair, Sally Wenzel, Klaus-Friedrich Rabe, Arnaud Bourdin, Njira L. Lugogo, Piotr Kuna, Peter Barker, Stephanie Sproule, Sandhya Ponnarambil, Mitchell Goldman, on behalf of the ZONDA study investigators

Rationale: Patients with uncontrolled asthma despite high-dosage inhaled corticosteroids plus long-acting β_2 -agonists (ICS/LABA) may need add-on oral corticosteroid (OCS) treatment to manage symptoms. However, frequent OCS use is associated with adverse effects. Benralizumab is a humanized, afucosylated, anti-interleukin-5 receptor α monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils. In Phase III trials,^{1,2} benralizumab significantly reduced annual exacerbation rates for patients with severe, eosinophilic asthma. The ZONDA trial (NCT02075255) evaluated OCS dosage-sparing effects of benralizumab for patients with severe asthma receiving high-dosage ICS/LABA and OCS.

Methods: In this RCT, 271 patients (aged 18–75 years) with severe, uncontrolled asthma (eosinophil counts ≥ 150 cells/ μL) receiving high-dosage ICS/LABA and OCS (7.5–40 mg/d) entered an initial 2- to 8-week run-in/optimization period during which their OCS dosage was titrated to the minimum effective dosage (baseline) without losing asthma control. Eligible patients were then randomized 1:1 to three 28-week treatment groups: benralizumab 30 mg SC either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses every 4 weeks) or placebo SC every 4 weeks. The treatment period comprised a 4-week induction phase (optimized OCS dosage maintained), a 20-week reduction phase (OCS dosage reduced), and a final 4-week maintenance phase (no further OCS dosage adjustment). Primary efficacy endpoint was percentage reduction from baseline in final OCS dosage while maintaining asthma control at Week 28. Annual asthma exacerbation rate was a secondary endpoint. Each benralizumab regimen was compared with placebo.

Results: Of 220 patients who were randomized and received treatment, 207 (94.1%) completed treatment. Benralizumab significantly reduced final OCS dosages by a median of 75% with the Q4W and Q8W regimens ($p < 0.001$) compared with placebo (25%). The odds of a reduction in OCS dosage were 4.09-times greater (Q4W; $p < 0.001$) and 4.12-times greater (Q8W; $p < 0.001$) than with placebo. Benralizumab also significantly reduced annual asthma exacerbation rates by 55% (Q4W; $p = 0.003$) and 70% (Q8W; $p < 0.001$) vs. placebo, despite reduction in OCS dosages in the active treatment groups (table). Adverse events were numerically lower for the benralizumab Q4W and Q8W groups vs. placebo (68.1% and 75.3% vs. 82.7%, respectively).

Conclusions: Benralizumab was well-tolerated and demonstrated significant, clinically relevant OCS-sparing benefits and asthma exacerbation rate reduction compared with placebo.

Supported by: AstraZeneca

An Itch for Berries: Blackberry-induced Urticaria Impact of Baseline Biomarkers on Exacerbation Rates in Adult Patients Initiating Omalizumab: Results from PROSPERO

Bradley E. Chipps, Noelle M. Griffin, Robert S. Zeiger, Amy Wagelie-Steffen, Allan T. Luskin, William Busse, Syed I. Mobin, Susan L. Limb, Benjamin L. Trzaskoma, Thomas B. Casale

Rationale: Clinical trials have consistently demonstrated a greater omalizumab effect on exacerbations in patients with higher levels of the Type 2 biomarkers: fractional exhaled nitric oxide (FeNO) and blood eosinophils. The present study evaluated whether a similar effect was seen in a real-world setting after initiation of omalizumab.

Methods: The PROSPERO (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab) study enrolled patients ≥ 12 years old with asthma who were identified by their physicians as candidates for omalizumab treatment. Patients had to have access to omalizumab through insurance or other funding and were followed for a maximum of 48 weeks. Asthma exacerbations and asthma control, assessed by the Asthma Control Test (ACT), were recorded at baseline and throughout the study. At baseline, 6 months, and the end of study, spirometry was performed and biomarkers (FeNO and eosinophils) were collected. Due to variability in biomarkers in adolescents, outcomes are reported for patients ≥ 18 years old, including changes from baseline in exacerbations rates, ACT score and lung function. Biomarker-high and -low groups are compared; p-values reflect adjustments for differences in baseline characteristics.

Results: 737 patients were ≥ 18 years; 563 (76.4%) patients completed 48 weeks of assessment. At baseline 35% of patients had eosinophils > 300 cells/ μL and 44% of patients had FeNO ≥ 25 ppb; 84.9% (612/721) of patients were uncontrolled (ACT < 20). At month 12, a mean (SD) rate of 0.8 (1.4) exacerbations/year was reported reflecting a clinically significant reduction (73%) from the 3.0 (3.3) rate reported in the 12 months prior to study entry. This reduction was irrespective of baseline FeNO or eosinophils. Patients also reported clinically significant improvements in asthma control; all biomarker subgroups achieved at least the minimal important difference of a 3-point improvement in ACT score. The difference between high and low eosinophils, with respect to ACT, was not clinically meaningful. Patients with high FeNO or high eosinophils demonstrated greater improvement in lung function as reflected by FEV₁ % predicted compared with those with low FeNO or eosinophils. (Table). Adverse events were consistent with the safety profile described in the current product label.

Conclusion: Patients experienced clinically significant reductions in asthma exacerbations following the introduction of omalizumab, regardless of their baseline Type 2 biomarker status. Although changes in FEV₁ % predicted were statistically significant, they were not clinically important.

Supported by: Genentech

Decreased Exacerbations and Hospitalizations in Adolescents Enrolled in PROSPERO (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab)

Allan T. Luskin, Noelle M. Griffin, Amy Wagelie-Steffen, Benjamin L. Trzaskoma, Susan L. Limb, William W. Busse, Robert S. Zeiger, Erika Gonzalez-Reyes, Thomas B. Casale, Bradley E. Chipps

Rationale: Prospective real-world data are important to supplement clinical trial data, especially in heterogeneous diseases like asthma. Data for adolescents are essential, as they are often under-represented in clinical trials.

Methods: 69 patients aged between 12-17 years old with asthma, identified as omalizumab candidates by their treating physicians and with access to omalizumab through insurance or other funding, were enrolled as part of the PROSPERO study. Patients were followed for a maximum of 48 weeks. At baseline and throughout the study, asthma-related healthcare utilization, including exacerbations, was recorded. Asthma control was recorded at each monthly visit using the Asthma Control Test (ACT). Spirometry was performed and biomarkers (FeNO, blood eosinophils) were collected at baseline, 6 months and end of study.

Results: 59 (86%) adolescents completed 48 weeks of the study; mean (SD) age 14.0 (1.69) years, primarily male (64%) and white (58%), with 33% Black or African American. On average, adolescents reported 2.8 exacerbations (67% with ≥ 2 exacerbations) that required oral corticosteroid use, ED visit or hospitalization in the 12 months prior to enrollment. 28% reported ≥ 1 asthma related hospitalization in the prior year. At month 12, a mean rate of 0.46 exacerbations per year was observed, representing an 84% reduction from baseline. 11.5% of patients reported ≥ 2 exacerbations and 4% reported ≥ 1 hospitalization, an 83% and 86% reduction from baseline, respectively. Mean (SD) baseline FEV₁ percentage predicted was 88% (17) and improved on average by 8% to 95% (20), which represents an absolute improvement of 160 mLs compared with baseline. 71.6% (48/67) of adolescent patients with baseline ACT data reported poorly controlled asthma at baseline based on ACT score of < 20 . At the study's conclusion, 68.8% of these poorly controlled patients were controlled (ACT ≥ 20). Baseline mean (SD) FeNO levels were 38.4 (39.4) ppb and mean (SD) eosinophils were 316 (210) cells/ μL , with 54.5% of patients having eosinophils ≤ 300 cells/ μL . Median (interquartile range) total IgE levels were 507 (960.7) IU/mL. At the end of study, mean (SD) FeNO levels decreased by 27% to 29.2 (28.1) ppb and mean eosinophils (SD) decreased by 34% to 209 (151) cells/ μL .

Adverse events were consistent with the safety profile described in the current product label.

Conclusion: In a real world setting, adolescents treated with omalizumab had significant improvements in asthma control as demonstrated by decreased exacerbations and hospitalizations, and improved ACT scores compared with baseline.

Supported by: Genentech

Cost-Effectiveness of Using FeNO in the Management of Asthma

Massanari M, Brooks EA, Rickard KA, Roman AA

Objective: Describe the cost-effectiveness of utilizing fractional exhaled nitric oxide (FeNO) to inform asthma management in comparison to the standard of care.

Introduction: In 2014, there were 17.7 million adults and 6.3 million children living with asthma in the US. Asthma guidelines recommend periodic assessment and management of symptoms to prevent exacerbations which may lead to hospitalization and increased healthcare costs. Some asthmatics have difficulty achieving disease control, and despite treatment with effective controller agents and biologics these patients experience an average of 2 exacerbations annually.

Methods: Using a decision analysis, the short-term cost-effectiveness of two alternatives to asthma management were compared: FeNO measurement in addition to standard of care management and the current standard of care. Model assumptions were drawn from the most recent literature pertaining to exacerbation frequency and severity as well as to medication and other medical resource utilization.

Results: Annual expected per-patient asthma management costs totaled \$2,013 for FeNO plus standard of care, and \$2,637 for standard of care alone. The use of FeNO to guide asthma management is expected to result in 0.077 additional QALYs per patient per year, rendering FeNO measurement as an adjunct to standard of care.

Conclusion: This cost-effectiveness assessment suggests that inclusion of FeNO measurement for guidance of asthma management would result in reduced risk for exacerbations and overall healthcare cost savings.

Supported by: Circassia

Measuring Exhaled Nitric Oxide (FeNO) Improves Assessment of Airway Inflammation and Guides Treatment Decisions

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Background: Assessment of patient's symptoms and lung function frequently underestimates asthma severity, airway inflammation and risk for an exacerbation. We hypothesized that adding fractional exhaled nitric oxide (FeNO) to the patient's clinical assessment will provide insights into underlying airway inflammation.

Method: Physicians were invited to participate if they had not used FeNO previously. Physician assessed the likelihood of airway inflammation using clinical measures after which FeNO was measured. Based on the FeNO result, physicians recorded what changes in drug therapy were made.

Results: Data from 337 physician practices which included 7,901 patients with asthma were included. Clinical impression of airway inflammation matched the actual FeNO in 4,457 patients. Anti-inflammatory treatment was changed based on FeNO in 30.7% patients. High FeNO group (83.90%) were on ICS, ICS/LABA or OCS therapy versus Low FeNO group (65.20%) who were on ICS, ICS/LABA or OCS therapy.

Conclusion: Assessing airway inflammation in asthma is improved by the measurement of FeNO at the point of care. This leads to clinically relevant changes in anti-inflammatory treatment. More frequently, clinicians stepped up steroids when FeNO was high compared to stepping down when FeNO was low. Additional research is needed to understand why inhaled corticosteroid treatment is not stepped down more frequently.

Supported by: Circassia

Efficacy of Recombinant Human C1 Esterase Inhibitor (rhC1INH) Across Anatomical Locations in Acute Hereditary Angioedema (HAE) Attacks

James W. Baker, Jonathan A. Bernstein, Joseph R. Harper, Anurag Relan, Marc A. Riedl

Introduction: rhC1INH is efficacious for acute HAE attacks. It is important to understand if differences in time to symptom relief may vary by anatomical attack location.

Methods: Data were pooled from 2 randomized, double-blind studies with open-label extensions. Patients ≥ 12 years of age with an acute HAE attack received rhC1INH 50 IU/kg or placebo. Time to beginning of symptom relief was defined as first timepoint that severity visual analog scale (VAS) score at an attack location decreased by ≥ 20 mm versus baseline with persistence. Data reported as mean (95% confidence interval).

Results: For all attack locations assessed, rhC1INH shortened time to beginning of symptom relief. Time to beginning of symptom relief for abdominal attack for rhC1INH (n=194) was 60.0 minutes (47.0, 62.0) and for placebo (n=15) was 240.0 minutes (45.0, 720.0). For peripheral attack, time to beginning of symptom relief for rhC1INH (n=169) was 105.0 minutes (90.0, 120.0) and for placebo (n=17) was 303.0 minutes (180.0, 720.0). Time to beginning of symptom relief for oro-facial-pharyngeal-laryngeal attack was 64.5 minutes (60.0, 120.0) for rhC1INH (n=36) and 306.0 minutes (30.0, 495.0) for placebo (n=6). For facial attack, time to beginning of symptom relief was 158.0 minutes (90.0, 330.0) for rhC1INH (n=24); placebo (n=2) could not be determined. For urogenital attack, time to beginning of symptom relief was 119.0 minutes (40.0, 270.0) for rhC1INH (n=13) and 320.0 minutes for placebo (n=1).

Conclusions: rhC1INH 50 IU/kg was efficacious in shortening time to symptom relief of acute HAE attacks, regardless of attack location.

Supported by: Pharming Healthcare Inc.

Randomized, Double-Blind, Placebo-Controlled Trial of Recombinant Human C1 Inhibitor for Prophylaxis of Hereditary Angioedema Attacks

Marc Riedl, MD; James W. Baker, MD; William H. Yang, MD; Richard F. Lockey, MD; Joseph R. Harper, PharmD; Anurag Relan, MD; Marco Cicardi, MD

Introduction: Recombinant human C1 inhibitor (rhC1INH) effectively treats acute attacks of hereditary angioedema (HAE). The purpose of this study was to evaluate rhC1INH as prophylaxis against acute HAE attacks.

Methods: In a phase 2, double-blind, 3-period crossover study, patients (≥ 13 years of age) with functional C1INH levels $< 50\%$ of normal and history of ≥ 4 HAE attacks during the preceding 3 months received intravenous rhC1INH 50 IU/kg (max, 4200 IU) once weekly (qw), twice weekly (biw), and placebo for 4 weeks, with a 1-week wash-out between treatments. The number of HAE attacks per 4-week treatment phase (primary endpoint) and the percentage of patients who had a clinical response ($\geq 50\%$ reduction in number of attacks from treatment with placebo to treatment with rhC1INH; secondary endpoint) were ascertained.

Results: Thirty-two patients were randomized. Mean patient age (standard deviation) was 45.9 (14.5) years, and most were female (81.3%). Mean number of HAE attacks was significantly reduced with rhC1INH biw (2.7 attacks, $P < 0.0001$) and qw (4.4 attacks, $P = 0.0004$) versus placebo (7.2 attacks). The percentage of patients who had a $\geq 50\%$ reduction in number of HAE attacks was greater with rhC1INH biw (74.2%; 95% CI, 57-86) than rhC1INH qw (41.9%; 95% CI, 26-59). The most commonly reported adverse events were headache (17.2% with biw rhC1INH, 6.9% with qw rhC1INH, 0% with placebo) and nasopharyngitis (0%, 10.3%, 7.1%). No thrombotic or thromboembolic events, drug hypersensitivity or anaphylaxis, or neutralizing antibodies were observed.

Conclusions: rhC1INH provided significant and clinically relevant reductions in HAE attack frequency and was well-tolerated.

Supported by: Pharming Healthcare Inc

Prevalence and Risk Factors for Persistent Very Poorly Controlled (VPC) Asthma after More Than a Decade in the TENOR II Cohort

B.E. Chipps, T. Haselkorn, R.S. Zeiger, E.R. Bleecker, S.J. Szeffler

Rationale: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR I) assessed severe/difficult-to-treat asthma patients. TENOR II (>10 years post-TENOR I) examined the prevalence of persistent very poorly controlled (pVPC) asthma.

Methods: TENOR II (N=341) was a multicenter, observational study with a single, cross-sectional follow-up visit in 2014. Asthma control was classified using NHLBI guidelines. pVPC asthma was defined as having VPC asthma at TENOR I and TENOR II enrollment visits; comparison group: well/not well-controlled asthma at either visit. Long-term predictors of pVPC asthma were assessed using multivariable logistic regression.

Results: A total of n=327 patients with an available level of asthma control at both time points were included. Nearly half (48.0%; n=157) had pVPC asthma. Mean (SD) pre- and post-bronchodilator FEV₁% predicted, were lower in pVPC than non-pVPC patients [62.5% (22.7%) versus 82.1% (15.7%), respectively, and 69.1% (22.3%) versus 86.5% (15.6%), respectively]. Total IgE geometric mean (95% CI): [89.3 (68.9, 115.8) versus 55.7 (38.8, 80.0)], and patients positive for any specific IgE (≥ 0.35 kU/L): 75.2% versus 70.2% were higher in pVPC than non-pVPC patients. In multivariable analyses, five variables measured at TENOR I enrollment were predictive of pVPC asthma: Black race (versus White), current and past smoking status (versus never smoked), FEV₁% predicted post-bronchodilator [per 10% decline] and corticosteroid course for worsening asthma in 3 months before enrollment.

Conclusions: pVPC asthma was highly prevalent in severe/difficult-to-treat asthma patients despite standard-of-care therapy. Several demographic and clinical factors were predictive of outcome in pVPC asthma.

Sponsored by: Novartis

Sonographic assessment of optimal needle length for epinephrine autoinjectors in infants and toddlers

Harold Kim, Chitra Dinakar, Paul McInnis, Xavier Benain, Dan Rudin, William Daley, Elke Platz

Rationale: Epinephrine autoinjectors (EAI) represent the standard of care for the treatment of anaphylaxis. Injections are most effective if epinephrine is delivered intramuscularly, whereas intraosseous injection may be harmful. The current needle length for pediatric EAI is 12.7 mm, however, the ideal needle length for infants and toddlers weighing 7.5 to 15 kg is unknown.

Methods: Infants and toddlers weighing 7.5-15 kg, recruited from two North American ambulatory allergy clinics underwent baseline and compression (10 pounds pressure) ultrasound of the anterolateral thigh with a modified ultrasound transducer mimicking the footprint and maximum activation force the EAI device (Auvi-Q®) would provide. Ultrasound images were analyzed offline, blinded to clinical data, for skin to bone (STBD) and skin to muscle distance (STMD) in short axis (transverse) approach.

Results: In 53 infants (mean age 19.5 months, 54.7% male, 81.1% Caucasian, mean weight 11.0 kg, mean height 79.3 cm, mean BMI 19.0 kg/m²) the mean baseline STBD was 22.8 mm (+/- 4.2) and the STMD was 8.2 mm (+/- 2.1). With 10 pounds compression, the mean STBD was 13.3 mm (+/- 2.1) and the STMD was 6.3 mm (+/- 1.2). A needle length of 12.7 mm would strike the bone in 43.1% of subjects during injection with 10 pounds compression in this population.

Conclusions: Our data suggests that the optimal needle length for an EAI for infants weighing 7.5 to 15kg should be shorter than the needle length in current, commercially available pediatric EAIs, in order to avoid striking the bone and possible intraosseous injections.

Sponsored by: Sanofi

Dupilumab Efficacy in Uncontrolled Persistent Asthma Patients With History of Comorbid Chronic Rhinosinusitis With or Without Nasal Polyps

Jorge F. Maspero, Constance Katelaris, Shyamalie Jayawardena, Paul Rowe, Jaman Maroni, Gianluca Pirozzi, Nikhil Amin, Neil M.H. Graham, Leda Mannent, Ariel Teper

Introduction: Dupilumab, a fully human anti-interleukin (IL)-4R α monoclonal antibody, inhibits signaling of IL-4 and IL-13, key drivers of type 2/Th2-mediated inflammation. In a pivotal phase 2b asthma study (NCT01854047), dupilumab 200/300 mg every 2 weeks (q2w) or every 4 weeks as add-on therapy to medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 -agonist (ICS+LABA) improved forced expiratory volume in 1 second (FEV₁), reduced severe asthma exacerbations, improved quality-of-life measures, and was generally well tolerated. This post hoc analysis evaluates efficacy of dupilumab on FEV₁ and severe exacerbations in the more difficult-to-treat subgroup of patients with history of comorbid chronic rhinosinusitis with/without nasal polyps (CRSwNP/CRSsNP), conditions often comorbid with asthma.

Methods: Change from baseline to Weeks 12 and 24 in FEV₁ (L) and annualized severe exacerbation rates in the 24-week treatment period are reported for 93 (20.0%) asthma patients with a clinical history of comorbid CRSwNP/CRSsNP, from the intent-to-treat population receiving placebo and dupilumab q2w doses currently being assessed in phase 3 (NCT02414854).

Results: Dupilumab q2w doses showed significant ($P < 0.01$ vs placebo) FEV₁ (L) improvement at Week 12 (200 mg 0.44; 300 mg 0.27 [Standard Error for both, 0.07]) and Week 24 (0.39; 0.34 [0.07]); dupilumab 200/300 mg q2w significantly ($P < 0.05$) reduced the rate of severe exacerbations, with reductions versus placebo of -72.3%/-87.8%, respectively.

Conclusions: Dupilumab 200/300 mg q2w as add-on to ICS+LABA therapy improved FEV₁ and reduced the rate of severe exacerbations in uncontrolled persistent asthma patients with history of comorbid CRSwNP/CRSsNP.

Sponsored by: Sanofi and Regeneron Pharmaceuticals, Inc.

Dupilumab Rapidly and Significantly Improves Lung Function and Decreases Inflammation by 2 Weeks After Treatment Initiation in Patients With Uncontrolled Persistent Asthma

Alberto Papi, Brian N. Swanson, Heribert Staudinger, Paul Rowe, Jaman Maroni, Shyamalie Jayawardena, Jennifer Hamilton, Nikhil Amin, Gianluca Pirozzi, Bolanle Akinlade, Neil M.H. Graham, Ariel Teper

Introduction: Dupilumab, a fully human anti-interleukin (IL)-4R α monoclonal antibody, inhibits signaling of IL-4 and IL-13, key drivers of type 2/Th2-mediated inflammation. In a pivotal phase 2b asthma study (NCT01854047), dupilumab as add-on to medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 -agonist improved forced expiratory volume in 1 second (FEV₁), reduced severe asthma exacerbations, improved quality-of-life measures, and was generally well tolerated. This post hoc analysis evaluates airway improvement and inflammation reduction at Week 2 following initial dupilumab loading doses.

Methods: Data are reported for patients receiving dupilumab 400 and 600 mg loading doses or placebo. Changes in FEV₁, forced vital capacity (FVC), forced expiratory flow of 25-75% (FEF_{25-75%}), fractional exhaled nitric oxide (FeNO), serum thymus and activation-regulated chemokine (TARC), and plasma eotaxin-3 from baseline to Week 2 were compared versus placebo. The proportion of patients achieving clinically meaningful improvements was assessed. Correlations between lung function and FeNO were computed.

Results: At Week 2, dupilumab 400 and 600 mg loading doses had significantly and equivalently improved FEV₁, FVC, and FEF_{25-75%} and reduced FeNO, TARC, and eotaxin-3 ($P < 0.001$ vs placebo). Clinically meaningful improvements in FEV₁, FVC, FEF_{25-75%}, and FeNO were evident in approximately 50% of patients. Changes in FeNO inversely correlated with FEV₁ ($r = -0.315$; $P < 0.0001$), FVC ($r = -0.222$; $P < 0.0001$), and FEF_{25-75%} ($r = -0.310$; $P < 0.0001$).

Conclusions: By Week 2, dupilumab induced significant and clinically meaningful improvements in lung function that correlated with reductions in inflammatory markers in adults with uncontrolled persistent asthma.

Sponsored by: Sanofi and Regeneron Pharmaceuticals, Inc.

Insights: A Quality Improvement Project

Marc Riedl, MD, Jason Raasch, MD, Leslie Vaughan, RPh,
Michelle Greer, RN, Elissa Ritt, MAS

Introduction: Immune globulin (IG) is indicated for the prevention of recurrent infection in primary immunodeficiency diseases (PID) but is occasionally used off-label with uncertain benefit. We performed a retrospective systematic review of clinical documentation for patients treated with IG for a diagnosis of PID to determine the quality of supportive evidence for the diagnosis and treatment.

Methods: We collected clinical and laboratory data submitted for insurance approval for patients prescribed IG. Anonymized data was reviewed by a panel of immunologists with expertise in PID. Panelists adjudicated diagnosis and appropriateness of therapy.

Results: 147 cases were reviewed: 112 female and 35 male, age range 19 – 81. Mean dosing was 0.49gm/kg monthly (STD 0.23), range 0.12-2 gm/kg. Reviewers found clinical data was frequently lacking detail to support the diagnosis or indication for IG therapy, specifically laboratory data or documented evidence of infection. Reviewers agreed 91 of 147 (62%) patients reviewed had a confirmed PID diagnosis with IG therapy appropriate for 61 (41%). Diagnostic concordance between prescribers and reviewers was most discrepant for common variable immune deficiency (CVID) patients, with reviewers identifying 28 cases of CVID compared to 86 identified by prescribers (32%).

Conclusions: Based on case review, expert immunologists found insufficient clinical and laboratory evidence to support IG therapy in 58% of cases reviewed. Improvements in diagnostic evaluation and clinical documentation may ensure IG therapy is secured in patients who require the life-saving therapy while reducing use in patients without PID, where the benefit is unproven.

Supported by: NuFactor Specialty Pharmacy

Adverse Events and Tolerability During Clinical Trials of the New Subcutaneous Immunoglobulin 20% Formulation (SCIG 20%) in Patients with PID in Europe and North America

D. Suez, G. S. Jolles, M. Stein, K. Paris, and L. Yel

Introduction: To present pooled safety and tolerability data of CUVITRU (subcutaneous immunoglobulin [SCIG] 20%), a ready-use liquid preparation of highly purified human IgG, from two phase 2/3 studies in patients with primary immunodeficiency diseases (PID) in Europe and North America.

Methods: The rate of causally-related AEs and tolerability were assessed in patients with PID aged ≥ 2 years with IgG trough levels >500 mg/dL at screening who were treated with SCIG 20% for ~ 12 months subsequent to ≥ 3 months of treatment with IVIG (North American study) or intravenous immunoglobulin (IVIG) or SCIG (European study). Patients received weekly SCIG 20% infusions up to 60 mL/site and 60 mL/hr/site.

Results: Overall, 91.8% (112/122) of patients aged 2-83 years who were treated with SCIG 20% completed the studies with only one discontinuation due to an AE (mild infusion site pain). Local AEs causally related to SCIG 20% were reported in 28.7% of patients with a rate of 0.034/infusion. Systemic AEs causally related to SCIG 20% were reported in 22% of patients (0.025/infusion); none of the AEs were severe. Most infusions were completed in <1 hour ($n=3445$; 53%) or <2 hours ($n=6005$; 92.4%). The majority of infusions (99.8% of 6665) were completed without slowing, interrupting, or stopping the infusion.

Conclusions: The new SCIG 20% demonstrated a low rate of local and systemic AEs at infusion volumes of up to 60 mL/site and infusion rates of up to 60 mL/h/site in patients with PID.

Supported by: Shire

Comparison of 40 IU/kg and 60 IU/kg Doses of Subcutaneous C1-Esterase Inhibitor (C1-INH [SC]) for the Prophylactic Treatment of Hereditary Angioedema (HAE): Efficacy Results From a Phase 3 Trial

Sandra Christiansen, MD, Henry Li, MD, PhD, Joseph Chiao, MD,
Iris Jacobs, MD

Introduction: HAE treatment guidelines recommend prophylaxis for patients with frequent and/or more disabling attacks or inadequate response to on-demand therapy. This phase 3 trial compared prophylaxis with C1-INH (SC) versus on-demand therapy only in patients with frequent HAE attacks.

Methods: In this randomized, multicenter, double-blind, crossover study, patients (≥ 12 years) experiencing ≥ 2 HAE attacks/month prior to study entry received twice-weekly C1-INH (SC) (40 IU/kg or 60 IU/kg) or placebo for 16 weeks and crossed over to the opposite treatment arm for 16 weeks. Patients used rescue medication as needed and recorded HAE symptoms daily. The primary efficacy endpoint was investigator-reported number of HAE attacks. Secondary endpoints included use of rescue medication and percentage of responders (patients with $\geq 50\%$ reduction vs placebo in number of HAE attacks). Attack severity was an exploratory endpoint.

Results: C1-INH (SC) 60 IU/kg had a greater treatment effect than 40 IU/kg on least squares mean of HAE attack frequency (0.52 vs 1.19 attacks/month), use of rescue medication (0.32 vs 1.13 uses/month), and percentage of responders (90.0% vs 76.2%). Patients on 60 IU/kg had half the number of attacks as patients on 40 IU/kg. The proportion of patients with ≥ 1 severe attack was lower with 60 IU/kg (8.9%) than with 40 IU/kg (20%).

Conclusion: In patients with ≥ 2 HAE attacks/month prior to study entry, C1-INH (SC) significantly reduced frequency and severity of HAE attacks as well as use of rescue medication compared with on-demand (placebo) only, with 60 IU/kg having a greater treatment effect than 40 IU/kg.

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Comparison of the Safety Profiles of 40 IU/kg and 60 IU/kg Doses of Subcutaneous C1-Esterase Inhibitor (C1-INH [SC]) in the Prophylactic Treatment of Hereditary Angioedema (HAE): Results from a Phase 3 Trial

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Introduction: In a phase 3 trial, prophylaxis with C1-INH (SC) 40 IU/kg and 60 IU/kg significantly reduced the number of HAE attacks versus placebo (on-demand therapy only) in patients with frequent HAE attacks, with the 60 IU/kg dose having a greater treatment effect. We compared the safety profile of these 2 doses based on adverse events (AEs) reported in this trial.

Methods: Safety assessment was a secondary objective. Study subjects were instructed to record the occurrence of AEs in their eDiary daily. At each study visit, investigators reviewed the eDiary with the subject. AEs, including injection-site reactions [ISRs] were recorded, including duration, time of onset, severity (mild, moderate, or severe), relationship to treatment, action taken, and outcome.

Results: Eighty-six patients and 5081 injections were evaluated. Of these, 12.1%, 4.9%, and 5.5% of injections were followed by an ISR for the 40 IU/kg, 60 IU/kg and placebo groups respectively. About 95% of ISRs were mild; none were serious or led to treatment discontinuation. There was no evidence of association between C1-INH (SC) dose and ISRs. There were no thromboembolic events, sepsis, or anaphylaxis reported and no inhibitory C1-INH antibodies or transmissions of viral infections.

Conclusions: Both 40 IU/kg and 60 IU/kg doses of C1-INH (SC) had favorable safety profiles and were well tolerated when administered twice weekly, with no evidence of dose-dependent safety concerns.

Supported by: CSL Behring

NAVIGATE II: A Randomized Double-Blind Trial of OPN-375, an Exhalation Delivery System with Fluticasone (EDS-FLU), for Treatment of Chronic Rhinosinusitis with Nasal Polyps (Nasal Polyposis)

John Messina, PharmD; Donald Leopold, MD, FACS; David Elkayam, MD; Per Djupesland, MD, PhD; Ramy Mahmoud, MD, MPH

Background: The EDS-FLU uses a new intranasal technology capable of significantly greater posterior/superior deposition than standard nasal sprays, particularly to the ostiomeatal complex where sinus ostia drain and polyps typically originate.

Methods: Randomized, 24 week (16 double-blind + 8 open-label), placebo-controlled study. Subjects (N=323, mean age=46, 87% prior intranasal steroids, 30% prior surgery) with CRSwNP and moderate-severe congestion were randomized to EDS-FLU doses of 93µg, 186 µg, or 372µg BID or EDS-placebo. All subjects received 372µg BID during the 8-week extension. Change in congestion scores (0-3) at week 4 and in bilateral polyp grade (0-6) at week 16 were co-primary endpoints.

Results: Changes in both co-primary endpoints (congestion and polyp grade) were significantly superior to placebo for each dose of EDS-FLU (p<0.001 vs placebo, all comparisons). Polyp reduction increased further through Week 24 (p<0.006 all comparisons vs placebo+372µg). After 24 weeks, polyps were eliminated in at least one nasal cavity in ~25-30% of subjects on EDS-FLU vs 8.7% in the placebo+372µg group (p≤0.014, all comparisons). SinoNasal Outcome Test (SNOT-22) improvement was superior in all EDS-FLU groups versus placebo (p<0.001), as were improvements in symptoms of rhinorrhea, facial pain/pressure, sense of smell, global impression of change and multiple measures of function and quality of life (p<0.05, all comparisons). The incidence of adverse events was similar to reports with traditional intranasal steroids.

Conclusions: EDS-FLU produced clinically and statistically significant improvement on multiple objective and subjective measures, and in patient-perceived outcomes demonstrating the advantages of targeted deposition from the intranasal exhalation delivery system.

Supported by: OptiNose

Enhanced Nasal Drug Delivery with New Exhalation Delivery Systems (EDS)

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Background: Achieving the full therapeutic potential of nasal drug delivery has been challenging due to unique characteristics of nasal anatomy and aerodynamics. New exhalation delivery systems (EDS) are being developed to overcome serious limitations of standard nasal sprays.

Methods: Patients deliver medication by exhaling through an EDS with a mouthpiece and specially shaped sealing nosepiece. Novel dynamics created by EDS delivery seal the soft palate, expand narrow nasal passages, and propel more drug to target sites beyond the nasal valve and above the inferior turbinate. Multiple studies were performed versus standard nasal sprays: in-vitro comparisons in anatomically correct casts; human in-vivo comparisons using acoustic rhinometry (AR), endoscopy, and radiolabeled vehicle to dynamically assess valve dimensions and deposition patterns.

Results: In vitro visualization and photometric analysis showed that an EDS for liquid fluticasone used in Phase-3 trials in chronic rhinosinusitis (CRS) with/without nasal polyps delivered more drug superiorly/posteriorly than standard nasal spray, notably including the middle meatus where sinuses drain/ventilate and polyps typically emerge. Dynamic assessment in humans of an EDS for powder found approximately threefold greater delivery to target sites in the upper posterior 2/3rds of the nasal cavity compared to conventional nasal spray {EDS-powder/spray mean(SD): 53.6%(18.5)/15.7%(13.9), p<0.02}. Similarly, an EDS for liquid produced approximately threefold higher deposition in the upper posterior half: EDS/Spray=32%(7.6)/11%(7.2), p<0.04). EDS also improved patency of the nasal valve region by AR and endoscopy.

Conclusions: EDS significantly improve drug deposition in the posterior/superior target sites in the nose that are therapeutically important, for example in treatment of CRS.

Supported by: OptiNose

Enhance-12: A One Year Study of Safety and Efficacy of OPN-375, an Exhalation Delivery System with Fluticasone (EDS-FLU), in Patients with Chronic Rhinosinusitis with and without Polyps (CRS w/s NP)

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Background: EDS-FLU delivers steroid with an intranasal technology capable of significantly greater posterior/superior deposition than standard nasal sprays, better reaching the ostiomeatal complex, most areas of the turbinates, and transition zones leading to the paranasal sinuses. Failure to effectively reach CRS target sites (especially the ostiomeatal complex) likely explains lack of efficacy and poor patient and physician satisfaction with standard steroid nasal sprays in CRS.

Methods: Multicenter, 52-week, open-label study with endoscopic assessment. Subjects with CRSw/sNP, defined by history and nasal endoscopy, received EDS-FLU 372µg BID. Lund-Kennedy assessments, nasal polyp grade, and local adverse events of interest were evaluated via nasal endoscopy. Other safety, efficacy and patient-rated outcomes were also assessed.

Results: 223 subjects enrolled (189 CRSsNP; 34 CRSwNP), 96% reported prior use of corticosteroids, and 29% prior surgery. EDS-FLU was well tolerated, with an adverse event profile similar to conventional nasal steroid sprays. Mean total SNOT-22 scores improved dramatically through 12 months: mean end-of-study change was -19.4 (CRSsNP) and -18.6 (CRSwNP). Among subjects with Lund-Kennedy edema scores >0 at baseline, 56% of CRSsNP and 50% of CRSwNP subjects had complete resolution of edema at end-of-study. Among subjects wNP, after 12 months 54.2% had polyp elimination in at least 1 nostril and 83.3% had ≥ 1 point improvement in polyp grade. 87% of patients reported improvement, and 72.1% reported 'much' or 'very much' improvement.

Conclusions: Over 1 year of treatment, EDS-FLU 372µg BID was well-tolerated and produced clinically significant improvements across a broad range of objective and subjective measures.

Supported by: OptiNose

NAVIGATE I: A Randomized Double-Blind Trial of OPN-375, an Exhalation Delivery System with Fluticasone (EDS-FLU), for Treatment of Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

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Background: EDS creates significantly different intranasal deposition than conventional nasal sprays. Deeper and broader distribution, especially to the ostiomeatal complex where sinus ostia drain and polyps typically originate, may optimize efficacy in CRS.

Methods: Patients diagnosed with CRSwNP and moderate-severe congestion were randomized to EDS-FLU (93µg, 186µg, or 372µg BID) or EDS-placebo for 24-weeks (16 double-blind + 8 open-label). All received EDS-FLU 372µg BID during the 8-week extension. Multiple endpoints, including all core CRS symptoms, were measured. Change in congestion score (0-3) at week 4 and summed bilateral polyp grade (0-6) at week 16 were co-primary endpoints. Change in Sino-Nasal Outcome Test-22 (SNOT-22) was a pre-specified, alpha-controlled key secondary.

Results: 323 patients enrolled (mean age=45, baseline SNOT-22=51, prior conventional intranasal steroid use=94%, prior surgery=35%). All EDS-FLU doses produced significantly greater improvement in both co-primary endpoints compared with placebo (polyp grade: placebo -0.45; EDS-FLU -0.96 to -1.06, p<0.05 all comparisons; congestion scores: placebo -0.24; EDS-FLU -0.49 to -0.62, p<0.05 all comparisons). EDS-FLU also significantly improved all 4 cardinal CRS symptoms, including anosmia/hyposmia, facial pain/pressure, rhinorrhea, and congestion/obstruction (p<0.05, all comparisons). Polyp grade continued to improve through 24 weeks. Changes in SNOT-22 score and Patient Global Impression of Change were superior in all EDS-FLU groups versus placebo (p<0.05, all comparisons). Surgical eligibility decreased from 56.9% to 23.2%. The safety profile was similar to conventional intranasal steroid nasal sprays.

Conclusions: EDS-FLU produced clinically and statistically significant improvement, as measured by a wide range of objective and subjective outcomes including all core symptoms and polyp grade.

Supported by: OptiNose

Major Allergen Content of SQ House Dust Mite SLIT-Tablets is Consistent and in Concordance with Patient Sensitivity Profiles in North America and Europe

Hendrik Nolte; Greg Plunkett; Mirko Bollen; Karin Grosch; Jørgen N. Larsen; Kaare Lund

Introduction: Consistency in composition and potency, particularly regarding major allergens, is crucial for allergen immunotherapy efficacy and safety. We compared allergen sensitivity profiles for house dust mite (HDM) in North American and European patients with the allergen content of commercially available US HDM extracts and SQ HDM sublingual immunotherapy (SLIT)-tablet (MK-8237; Merck/ALK).

Methods: Sensitivity towards Der p 1, Der p 2, and Der p 10 was determined in randomly selected subgroups (n=220) from European and North American SQ HDM SLIT-tablet trials. Der 1/Der 2 ratios were determined in 10,000 and 30,000 AU/mL HDM extracts from 5 US companies. SQ HDM SLIT-tablets are produced by mixing body and fecal fractions of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* to achieve a 1:1:1:1 ratio between Der f 1/2 and Der p 1/2 allergens. Allergen content was analyzed by ELISA and compared with in-house references.

Results: Subject sensitization profiles indicated high reactivity frequencies towards Der p 1 and Der p 2 regardless of geographic region. Average Der 1/Der 2 ratios in US extracts ranged from 0.4 to 18.0. For SQ HDM SLIT-tablet (20 batches), normalized mean (SD) content for Der f 1, Der p 1, and combined Der 2 allergens was 1.000 (0.119), 1.000 (0.061), and 1.000 (0.064) units, respectively. Other HDM allergens were also present.

Conclusions: Der 1/Der 2 are major HDM allergens in North America and Europe. The described process enables content control of each major allergen resulting in SQ HDM SLIT-tablets containing both mites, and consistent and equivalent Der 1/Der 2 content.

Supported by: Merck

Efficacy and Safety of the SQ House Dust Mite Sublingual Immunotherapy Tablet in North American Children and Adults: Findings from a Large Randomized, Placebo-Controlled Clinical Trial

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Introduction: SQ house dust mite (HDM) sublingual immunotherapy (SLIT)-tablet (MK-8237; Merck/ALK) demonstrated beneficial effects on allergic rhinitis and asthma, but previous trials were conducted in European subjects. This is the largest trial to assess efficacy/safety of HDM SLIT-tablets in North American subjects with HDM allergic rhinitis with/without conjunctivitis (AR/C).

Methods: In this double-blinded, multicenter trial (NCT01700192), 1,482 subjects (aged ≥ 12 years) with HDM AR/C with or without asthma were randomized to daily 12 SQ-HDM SLIT-tablet or placebo for up to 52 weeks. Subjects had a rhinitis daily-symptom score (DSS, 4 nasal symptoms, maximum=12) of ≥ 6 , or ≥ 5 with 1 severe symptom, on 5 of 7 consecutive days before randomization. The primary endpoint was average total combined rhinitis score (TCRS), defined as rhinitis DSS plus rhinitis daily-medication score (DMS), during the last 8 weeks of treatment.

Results: Treatment with 12 SQ-HDM SLIT-tablet improved TCRS 17% vs placebo (95% CI: -25%, -10%). Improvements vs placebo in the secondary endpoints average rhinitis DSS, rhinitis DMS, total combined rhinoconjunctivitis score, and ARC symptoms assessed by visual analogue scale were 16%, 18%, 17%, and 16%, respectively. All nominal P-values were < 0.001 vs placebo except rhinitis DMS. No treatment-related AEs meeting the ICH definition of serious were reported; 1 treatment-related systemic allergic reaction occurred (assessed as moderate) at first administration under medical supervision and was treated with epinephrine.

Conclusions: 12 SQ-HDM SLIT-tablet was well-tolerated and improved HDM ARC symptoms in adults and children. This was the first successful North American trial of a HDM SLIT-tablet.

Supported by: Merck

Onset of Action of House Dust Mite Sublingual Immunotherapy Tablet (SLIT-Tablet) Using an Environmental Exposure Chamber

Friedrich Horak; Jennifer Maloney; Harold S. Nelson; David I. Bernstein; Petra Ziegelmayer; René Ziegelmayer; Patrick Lemell; Hendrik Nolte

Introduction: Onset of the clinical effect of sublingual allergen immunotherapy with house dust mite (HDM) is undetermined. A HDM environmental exposure chamber trial was conducted to characterize onset of action and dose-related efficacy of MK-8237 (Merck/ALK-Abelló) HDM SLIT-tablet.

Methods: In this randomized, double-blind, single-site trial adults with HDM-induced allergic rhinitis with/without conjunctivitis and/or asthma (n=124) received daily 12 SQ-HDM, 6 SQ-HDM, or placebo for 24 weeks, and underwent HDM exposure challenges (6 hours) at baseline and weeks 8, 16, and 24. Total nasal symptom score (TNSS) at week 24 vs placebo was the primary endpoint. TNSS was the sum of 4 nasal symptoms (maximum score=12).

Results: TNSS improvement with MK-8237 versus placebo was observed at weeks 8 (mean difference: -1.37, 20.3%; $P=0.07$), 16 (mean difference: -2.08, 30.1%; $P<0.001$) and 24 for the 12 SQ-HDM dose, and weeks 16 (mean difference: -1.23, 17.8%; $P=0.32$) and 24 for the 6 SQ-HDM dose. Effects of both doses increased throughout the study, with 48.4% and 26.2% improvement, respectively, in TNSS at week 24 versus placebo (mean difference: -3.62, $P<0.001$ and -1.98, $P=0.03$). Significant increases in specific IgE and IgG4 paralleled the clinical improvement. Both doses of MK-8237 were well tolerated, with no systemic allergic reactions or reactions requiring epinephrine.

Conclusions: Onset of action for HDM SLIT-tablet was dose-dependent, with the 12 SQ-HDM and 6 SQ-HDM doses first exhibiting significant efficacy after 8 and 16 weeks of treatment, respectively. The treatment effect increased over time, with maximal efficacy at week 24.

Supported by: Merck

Comparison of Relative and Absolute Treatment Differences Between Sublingual Immunotherapy Tablets and Pharmacotherapies for Seasonal and Perennial Allergic Rhinitis: Pooled Analyses of Clinical Trials

Peter S. Creticos; Stephen Durham; Harold S. Nelson; Amarjot Kaur; Eli O. Meltzer; Hendrik Nolte

Introduction: These analyses indirectly compare effects on nasal symptoms with sublingual immunotherapy (SLIT)-tablets vs pharmacotherapies for seasonal and perennial allergic rhinitis (SAR and PAR) using standardized mean difference (SMD) or difference relative to placebo.

Methods: A fixed-effect meta-analysis method estimated treatment differences in average total nasal symptom scores (TNSS) from pooled data collected in 6 Timothy grass SLIT-tablet (n=3,094), 2 ragweed SLIT-tablet (n=658), and 2 house dust mite (HDM) SLIT-tablet trials (n=1,768) versus 7 montelukast (10 mg; n=6,799), 9 desloratadine (5 mg; n=4,455), and 8 mometasone furoate nasal spray (MFNS; 200 μ g QD; n=2,140) SAR or PAR trials.

Results: In grass and ragweed SLIT-tablet trials, the relative average improvement in TNSS versus placebo was 16.3% (SMD, -0.26) and 17.1% (SMD, -0.29), respectively. In HDM SLIT-tablet trials, TNSS relative improvement versus placebo was 16.1% (SMD, -0.24). In montelukast, desloratadine, and MFNS trials, TNSS relative improvement versus placebo was 5.4% (SMD, -0.18), 8.5% (SMD, -0.25), and 22.2% (SMD, -0.61), respectively, for SAR trials, and 3.7% (SMD, -0.12), 4.8% (SMD, -0.13), and 11.2% (SMD, -0.28) for PAR trials.

Conclusions: Based on relative effect vs placebo, grass and ragweed SLIT-tablets had a comparable effect vs MFNS and were numerically superior to montelukast and desloratadine for SAR. HDM SLIT-tablet elicited similar or greater improvement than all evaluated pharmacotherapies for PAR. SMDs indicated the same effect size as relative differences among pharmacotherapies, but underestimated effect size for SLIT-tablets, likely due to trial design characteristics such as allowed rescue medication use by placebo patients in SLIT-tablet studies.

Supported by: Merck