Eastern Pulmonary Conference
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All Scientific Posters will be on display in the Ponce de Leon Foyer beginning Friday morning, September 9th. Authors of these posters are requested to be at their poster to discuss their work from 9:30 – 10:30 AM, both Friday and Saturday.

Not for CME Credit

Long-term Safety of Flunisolide HFA in Adult, Adolescent, and Pediatric Patients with Asthma

Renee Bomar, MSN, CPNP; Jonathan Corren, MD

Introduction. Three studies evaluated the long-term safety of flunisolide HFA (Aerospan®) via assessments of HPA-axis suppression (adults, adolescents and pediatric patients) and growth (pediatric patients) in patients with asthma.

Methods. Adults and adolescents 12 and older with mild-to-moderate asthma were studied in a 52-week, randomized, open-label, active-controlled trial. Patients were treated with flunisolide HFA 80-320 µg BID, or beclomethasone 126-336 µg BID for 52 weeks and underwent cosyntropin stimulation at baseline, week 26, and week 52. Two 52-week trials evaluated adverse events, impact on HPA-axis, and changes in growth velocity with the 160 mcg dose of flunisolide HFA in patients 4 to 11 years. The first trial was open-label and included cromolyn (1600 µg qid as a negative control) and beclomethasone (168 µg bid as a positive control), while the second was double-blind and placebo-controlled in patients 4 to 9.5 years old.

Results. In the adult and adolescent trial, there were no effects on urinary cortisol. In the open-label pediatric trial, no HPA axis suppression was seen in 84 patients where HPA-axis function was assessed. Growth velocity of 6.2 cm/52 weeks was reported for flunisolide HFA (compared with 5.3 cm/52 weeks and 6.9cm/52 weeks for beclomethasone and cromolyn, respectively). In the placebo-controlled pediatric trial, non-significant changes in growth velocity (6.19 cm/52 weeks for placebo compared to 6.01 cm/52 weeks for flunisolide HFA; p= 0.425) were reported.

Conclusion. In three 52-week trials in adults, adolescents, and pediatric patients with mild-to-moderate asthma, there was no significant impact on HPA-axis assessments and growth velocity with flunisolide HFA.

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Efficacy of Flunisolide HFA in Adult and Adolescent Patients 12 Years and Older with Asthma by Baseline Inhaled Steroid

Alison Martens, RN, BSN, CCRP; Jonathan Corren, MD

Introduction: Flunisolide HFA (Aerospan®), a small particle ICS with an integrated spacer, is approved for treatment of asthma in patients 12 years and older at daily doses of 160 mcg (2 puffs) and 320 mcg (4 puffs). A retrospective analysis of a pivotal flunisolide HFA clinical trial evaluated efficacy based on each patient's prior use of inhaled corticosteroids (ICSs).

Methods: This was a randomized, double-blind trial of flunisolide HFA (80, 160 and 320 mcg BID) and flunisolide CFC (250, 500 and 1000 mcg BID) vs placebo for 12 weeks in patients 12 years and older with mild-to-moderate asthma. The primary efficacy endpoint was change from baseline in % predicted FEV_1. The retrospective analysis by baseline ICS included fluticasone (n=195), beclomethasone (n=190), triamcinolone acetonide (n=174) and flunisolide (n=98).

Results: Of the 669 randomized patients, 548 (82%) completed the trial. Improvement in FEV_1 was approximately 12% after a 2week run-in with flunisolide CFC. After 12 weeks, patients treated with flunisolide HFA 160 mcg BID maintained the 12% improvement achieved during run-in, patients treated with 320 mcg BID had a 0.4% improvement over run-in, and patients treated with placebo had a 4.5% decrease ($p<0.007$; active HFA treatments vs placebo). LS mean changes from baseline in % predicted FEV_1 did not significantly differ based on previous ICS.

Conclusion: The results suggest that the efficacy with flunisolide HFA 160 and 320 mcg BID is at least equivalent to other ICSs, as demonstrated by similar % improvements in FEV_1 for each of the baseline ICS subgroups.

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Association of Vitamin D deficiency with Pulmonary Dysfunction in Non-Cystic Fibrosis Bronchiectasis

James B. Gleason, Shane Bobart, Chris D'Angelo, Anas Hadeh

Background: In chronic lung conditions such as Non-Cystic Fibrosis Bronchiectasis (NCFB), a debilitating disease with recurring bacterial infections, vitamin D deficiency is common. Studies have correlated serum vitamin D levels and pulmonary dysfunction in Cystic Fibrosis, a condition that universally leads to bronchiectasis, suggesting that vitamin D deficiency may contribute to more rapid pulmonary function decline. Furthermore, patients with NCFB who are vitamin D deficient are more frequently colonized with bacteria and have more frequent exacerbations. Various studies have demonstrated the role of vitamin D in innate immunity by upregulation of potent antimicrobial peptides against Pseudomonas aeruginosa, reduction of pro-inflammatory cytokine production, and anti-inflammatory function associated with Th1/Th2 balance. Currently, the effect of Vitamin D on pulmonary function in NCFB is unclear, as such; we investigated the role of Vitamin D in NCFB.

Methods: After approval by the IRB, a retrospective chart review was performed. Data was abstracted from clinically stable NCFB patients under care of the Cleveland Clinic Health Systems 9 regional hospitals and 21 family health centers who had spirometry and serum 25-hydroxyvitamin D [25(OH)D] levels obtained within 3 months of one another.
Collected variables included 25(OH)D level, spirometric parameters, demographics, BMI, cause of bronchiectasis, A1AT testing, chronic comorbidities, medications and previously cultured pathogens such as P. aeruginosa.
Statistical analysis included frequencies and means for each variable and across categories, analysis of variance to examine the effect of each of the variables on 25(OH)D levels, Pearson correlations between 25(OH)D and either percent predicted FEV1 or FVC for each subpopulation. Analysis of covariance was used to examine whether these correlations differed significantly, and multiple regression to examine the relationship between 25(OH)D and pulmonary function.

Results: Enrollees from 2015 totaled 123. Overall mean 25(OH)D level was 32.81 ng/ml. Serum 25(OH)D levels showed a statistically significant correlation with FEV1 % predicted ($r = 0.31$, $p < 0.001$) and FVC % predicted. Significant variations in FEV1 % predicted among Serum 25(OH)D groups was identified ($p = 0.002$ and $p = 0.008$). Subpopulation analysis of covariance identified systemic antibiotic use as a marginally significant modifier of the correlation between 25(OH)D level and FEV1 % predicted. Multiple regression with 12 potential predictors demonstrated 25(OH)D to be an independent predictor of FEV1 % predicted ($p < 0.05$).

Conclusions: Serum 25(OH)D levels are significantly associated with pulmonary function in NCFB suggesting that Vitamin D is an important a cofactor for determining lung function in this disease population.

Asthma in the Elderly: The Effect of Montelukast

Michele Columbo, M.D.

Introduction: Little is known about asthma in the elderly as most asthma studies have not examined this patient group. It is unclear whether leukotriene antagonists benefit older asthmatics. We studied the effect of montelukast in elderly asthmatics.

Methods: This is a double-blind, placebo controlled, cross-over study. Twenty-five subjects 65 years old and older were evaluated at week 0, 1, 5, 9, 13, and 17. Each subject received montelukast 10 mg and placebo each for 8 weeks. The results are expressed as the mean ± SD and analyzed by two tailed t test.

Results: Mean age was 72.9±4.9 years, 20/25 subjects were atopic, 18/25 had rhinitis, 22/25 were using inhaled steroids, 18/25 long-acting bronchodilators, 5/25 tiotropium. Baseline Asthma Control Test (ACT) score was 22.9±2.1, daily symptom score 0.3±0.6, puffs of albuterol were 0.1±0.3/day. FEV1% was 81.2±15.8%, FEV1/FVC 0.74±0.1, and FEF25-75% 78.2±31.5%. Peripheral blood eosinophils were 0.38±0.25 K/UL, serum IgE 182±248 U/ml. Montelukast for 4 or 8 weeks did not affect ACT, daily symptom scores, puffs of albuterol/day, spirometric values, eosinophils, or IgE vs. baseline or placebo ($p>0.28$). In subjects with baseline peripheral blood eosinophil counts ≥0.6K/UL (0.83±0.22, n=4), montelukast reduced such counts vs. placebo (0.54±0.11 vs. 1.22±0.5, $p=0.037$).

Conclusions: In this study of elderly asthmatics, montelukast had no effect on ACT and daily symptom scores, number of puffs of albuterol, spirometric values, peripheral blood eosinophils or serum IgE. Montelukast reduced peripheral blood eosinophils in subjects with higher eosinophil counts. These results will require confirmation in larger patient cohorts and in patients with uncontrolled asthmatic symptoms.

Cardiovascular Risk Factors, Comorbidities and Concomitant Medications From Three Phase 3 Trials of Pirfenidone in Idiopathic Pulmonary Fibrosis (IPF)

Marilyn K. Glassberg, Steven D. Nathan, John Stauffer, Willis Chou, Paul W. Noble

Introduction: Pirfenidone is an oral anti-fibrotic agent approved for the treatment of IPF. Patients with IPF often have cardiovascular risk factors and comorbidities and take related concomitant medications. We describe cardiovascular risk factors, comorbidities and related concomitant medications in patients enrolled in the three pirfenidone Phase 3 trials.

Methods: This analysis pooled all patients randomized to pirfenidone or placebo in ASCEND or CAPACITY. Medical history at baseline and concomitant medication use during treatment were reported by investigators. Patients with unstable/deteriorating cardiac disease within the past 6 months were excluded from enrollment. Cardiovascular comorbidity rates from the literature were compared with rates from the trials.

Results: 1334 patients (779 from CAPACITY and 555 from ASCEND) were included. The mean age was 67 years, 74% were male and 66% were former/current smokers. Other commonly reported cardiovascular risk factors were hypertension (52%), hypercholesterolemia (24%), hyperlipidemia (22%), diabetes (20%), sleep apnea syndrome (15%) and obesity (6%). Cardiac disorders as a system organ class were reported in 36% of patients at baseline, including coronary artery disease (17%), myocardial infarction (7%), atrial fibrillation (5%) and angina pectoris (3%). Deep vein thrombosis and pulmonary embolism were reported in 2% and 1% of patients, respectively. These findings were consistent with published literature (INSIGHTS-IPF, IPF-PRO and PASSPORT registries), although actual rates varied. Concomitant cardiovascular medications used during treatment included: lipid-modifying agents (60%); anti-thrombotics such as anti-platelets (including acetylsalicylic acid) and anti-coagulants (55%); renin-angiotensin inhibitors (39%); beta-blockers (26%); diuretics (22%); anti-diabetic drugs (20%); and calcium-channel blockers (18%).

Conclusions: Cardiovascular risk factors, comorbidities and concomitant medication use are common in patients with IPF, including those enrolled in the Phase 3 trials of pirfenidone and in real-world observational registries. Awareness of cardiovascular risk factors, comorbidities and concomitant medications is an important consideration in the management and treatment of patients with IPF.

Funded by Genentech

Cardiovascular and Bleeding Events in Phase 3 Trials of Pirfenidone in Idiopathic Pulmonary Fibrosis (IPF)

Marilyn K. Glassberg, Steven D. Nathan, John Stauffer, Willis Chou, Paul W. Noble

Introduction: Pirfenidone is an approved anti-fibrotic agent for IPF treatment. Patients with IPF often have cardiovascular comorbidities and/or risk factors. To understand pirfenidone's impact on cardiovascular risk, we described the occurrence of cardiovascular and bleeding adverse events (AEs) in patients with IPF enrolled in three pirfenidone Phase 3 trials.

Methods: Treatment-emergent cardiovascular and bleeding AEs (including ≤28 days post-treatment) in CAPACITY and ASCEND were retrospectively reviewed. Occurrences of major adverse cardiac events (MACE) which included stroke, myocardial infarction (MI), unstable angina and cardiac arrest were identified. Patient incidence of cardiovascular and bleeding events was summarized for pirfenidone 2403 mg/day and placebo patients. Patients with a history of unstable or deteriorating cardiac disease within the past 6 months were excluded from enrollment.

Results: 1247 patients were included; 623 received pirfenidone and 624 received placebo. Between the pirfenidone and placebo groups: mean age was 68.0 years for both, 74.3% and 74.5% were male and 66.5% and 64.2% were current/former smokers, respectively. The cardiovascular risk profile at baseline was generally similar between pirfenidone and placebo, including history of coronary artery disease (15.6% vs. 15.7%) and MI (5.1% vs. 5.3%); more placebo patients had hypertension (53.8% vs. 49.1%). In pirfenidone and placebo, concomitant anti-thrombotic agents were administered to 51.2% and 57.2% of patients, and concomitant lipid-modifying agents to 60.7% and 59.9%, respectively. Mean exposure to pirfenidone and placebo was 14.1 and 14.3 months, respectively. The incidence of MACE (1.4% and 2.1%) and bleeding events (3.7% and 4.3%) was similar between groups.

Conclusions: The incidence of MACE or bleeding events was similar between pirfenidone and placebo patients in these trials. This post-hoc analysis suggests that pirfenidone did not increase the risk of cardiovascular and bleeding events over a mean study drug exposure of ≈14 months in the Phase 3 clinical trial population compared with placebo.

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Safety of Pirfenidone With Idiopathic Pulmonary Fibrosis (IPF) in a United States (US) Expanded Access Program (EAP)

Lisa Lancaster, Alexander Auais, Beiying Ding, Ahmar Iqbal, Lake Morrison

Introduction: The anti-fibrotic agent pirfenidone was approved in the US in 2014 to treat IPF. We examined safety events in patients with IPF in the US who received early access to pirfenidone.

Methods: EAP was a multicenter study at 92 US sites that allowed patients with IPF access to pirfenidone (recommended dose, 801 mg 3 times/day) prior to approval. Patient visits occurred between April 14, 2014, and May 15, 2015, with a maximum follow-up of 11.3 months. Eligible patients had clinical and radiographic diagnosis of IPF, including a definite or possible usual interstitial pneumonia (UIP) pattern, percent predicted forced vital capacity ≥ 50 and percent predicted carbon monoxide diffusing capacity ≥ 30. Data on adverse drug reactions (ADRs, defined as adverse events [AEs] deemed causally related to pirfenidone) and changes in clinical laboratory parameters were analyzed.

Results: Of the 1620 patients, 1221 (75.4%) completed the program. Mean (SD) age was 71.0 (7.7) years, and 74.7% were male. 66.5% had definite UIP, and 33.2% had possible UIP. Mean (SD) duration of pirfenidone exposure was 22.8 (9.6) weeks; mean (SD) daily dose was 2058.7 (399.2) mg. ADRs were reported in 64.9%, with 3.3% reported as severe and 0.2% as life threatening. The most common ADRs were nausea (22.6%), fatigue (19.6%), diarrhea (11.2%) and rash (8.2%). ADRs leading to withdrawal occurred in 13.0%, most commonly nausea (2.7%). Serious ADRs occurred in 24 patients (1.5%), primarily elevated liver function tests (0.6%), diarrhea (0.1%) and nausea (0.1%), with no deaths reported.

Conclusions: In this study of patients with IPF, including those with possible UIP, the safety profile of pirfenidone was consistent with earlier clinical trials that primarily enrolled patients with definite UIP; no new safety signals were identified. The ADRs reported in this study were similar to the AEs reported in previous pirfenidone clinical trials.

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Reduction in Non-Elective Respiratory-Related Hospitalizations in Patients Treated With Pirfenidone: Pooled Analyses From Three Phase 3 Trials of Pirfenidone in Idiopathic Pulmonary Fibrosis

Brett Ley, Jeffrey Swigris, John Stauffer, Willis Chou, Harold R. Collard

Introduction: Patients with idiopathic pulmonary fibrosis (IPF) are frequently hospitalized for a variety of reasons. Respiratory-related hospitalizations may occur because of acute exacerbations of IPF, respiratory tract infections, respiratory failure and other causes. Regardless of cause, respiratory-related hospitalizations have been linked to poor outcomes in patients with IPF. We describe the proportion of patients from the three Phase 3 pirfenidone IPF trials with at least one non-elective hospitalization (all-cause, respiratory-related and non-respiratory-related) over 12 months.

Methods: In three Phase 3 randomized, placebo-controlled studies of pirfenidone for IPF (CAPACITY I/II and ASCEND), patients were randomized to pirfenidone (2403 mg/day) or placebo. In the two CAPACITY studies, respiratory-related hospitalizations were a pre-specified endpoint. In ASCEND, hospitalizations were reported as adverse events (AEs), and retrospectively categorized as respiratory-related or non-respiratory by case review. The pooled rates of patients experiencing ≥1 non-elective hospitalization (all-cause, respiratory-related and non-respiratory-related) for pirfenidone and placebo patients over 12 months are summarized. Rate of death post-hospitalization was also reported.

Results: A total of 1,247 patients (692 CAPACITY and 555 ASCEND) were included. In pooled analyses, the proportion of patients experiencing ≥1 all-cause hospitalization over 12 months was no different between pirfenidone and placebo-treated patients. The proportion of patients experiencing ≥1 respiratory-related hospitalization was 12% in the placebo group vs 7% in the pirfenidone group (odds ratio 0.56; *P*=0.004). Deaths after hospitalization were numerically reduced in the pirfenidone group, most substantially for respiratory-related hospitalizations.

Conclusion: Patients with IPF frequently require hospitalization for a variety of reasons. Pirfenidone may reduce the risk of non-elective respiratory-related hospitalizations over 12 months.

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Effect of Continued Treatment with Pirfenidone Following a ≥10% Relative Decline in Percent Predicted Forced Vital Capacity (%FVC) in Patients with Idiopathic Pulmonary Fibrosis (IPF)

Steven D. Nathan, Marilyn K. Glassberg, Lisa Lancaster, David J. Lederer

Introduction: A pooled analysis of three Phase 3 trials showed that patients who experienced a ≥10% absolute decline in %FVC during the first 6 months of treatment had clinical benefit with continued pirfenidone treatment in the subsequent 6 months (Nathan et al., ATS 2015). To further explore the potential benefit of continued pirfenidone treatment, we assessed subsequent outcomes after a ≥10% relative decline in %FVC during the first 6 months of treatment.

Methods: Data included all patients randomized to pirfenidone 2403 mg/day or placebo in ASCEND or CAPACITY (N=1247). Patients with a ≥10% relative decline in %FVC were selected by the 6-month study visit. Patients in the pirfenidone and placebo groups who experienced any of the following during the subsequent 6-month interval were compared: (1) ≥10% relative decline in %FVC or death; (2) death; or (3) no further decline in %FVC.

Results: Of the patients that experienced an initial ≥10% relative decline in %FVC, 80 and 140 patients received pirfenidone and placebo, respectively. In the subsequent 6 months, 17 (21.3%) and 50 (35.7%) patients in the pirfenidone and placebo groups, respectively, experienced a ≥10% relative decline in %FVC or death. More patients receiving pirfenidone had no further decline in %FVC and fewer patients died compared with placebo during the subsequent 6-month interval.

Conclusions: In patients who experienced ≥10% relative decline in %FVC during the first 6 months of treatment, continued treatment with pirfenidone appeared to lower the risk of %FVC decline or death during the subsequent 6 months, similar to previous results observed with ≥10% absolute %FVC cutoff. Using ≥10% relative FVC decline identified more than twice as many patients compared to using absolute change. These findings suggest a potential benefit of continued treatment with pirfenidone despite an initial clinically meaningful decline in FVC ≥10% regardless of calculation method.

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Baseline IgE Levels as a Marker of Type 2 Asthma Among Patients Enrolled in the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO)

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Objective: To determine the relationship of immunoglobulin E (IgE) to other type 2 biomarkers and patient-reported outcomes in patients with moderate-severe/difficult-to-control asthma.

Methods: Total serum-IgE, fractional exhaled nitric oxide (FeNO), and peripheral blood eosinophils (EOS) were measured at baseline in 737 patients (≥18 years) in an omalizumab registry. Asthma control (Asthma Control Test [ACT]) and health-related quality of life (Asthma Quality of Life Questionnaire [AQLQ]) were assessed. Spearman correlation coefficients (r_s) between IgE and other biomarkers, ACT, AQLQ and airway reversibility as measured by pre- and post- bronchodilator FEV_1 were determined.

Results: Median (range) baseline biomarker values were: IgE, 170.6 IU/mL (1.1-8659 IU/mL, n=677); FeNO, 22.0 ppb (2.0-266 ppb, n=722); EOS, 230/µL (0-2340/µL, n=622). Median ACT and AQLQ were 13.0 (5-25, n=697) and 3.9 (1-7, n=702), respectively. Mean baseline pre-bronchodilator FEV_1 was 74.7% of predicted (n=728); mean (SD) bronchodilator reversibility was 8.65% (16.35, n=711). One or more high Type 2 biomarkers were noted in a substantial proportion of patients; EOS ≥300/uL (37%), FeNO ≥25 ppb (45%). IgE weakly correlated with EOS or FeNO. EOS, FeNO and IgE correlated with airway reversibility. A weak relationship between IgE levels, Eos, and FeNO and ACT scores was noted.

Conclusion: The relationships of total serum IgE to other type 2 biomarkers are weak in this cohort but generally consistent with published data. IgE performs similarly to other Type 2 biomarkers with respect to airway reversibility and correlation with ACT. Further analyses will determine the relationship of the biomarkers to omalizumab response.

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Economic Burden of Impairment in Children with Severe or Difficult-to-Treat Asthma

S. J. Szefler, R. S. Zeiger, T. Haselkorn, D. R. Mink, B. E. Chipps

INTRODUCTION: We sought to assess the association between asthma-induced impairment and burden of costs in children with severe or difficult-to-treat asthma.

METHODS: Children aged 6-12 years with severe or difficult-to-treat asthma enrolled in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens study who had data available corresponding to the impairment domain of the National Heart, Lung, and Blood Institute guidelines at baseline, month 12, and month 24 visits were included (n=628). Children were categorized into three asthma cohorts based on impairment—very poorly controlled, not well controlled, and well controlled—using symptoms, medication use, nighttime awakenings, interference with normal activity, and pre-bronchodilator forced expiratory volume in 1 second or peak flow. Outcomes were costs associated with number of school days lost, unscheduled physician visits, emergency department visits, and overnight hospitalizations.

RESULTS: Impairment classification of the children at baseline included 61.5% very poorly controlled, 34.9% not well controlled, and 3.7% well controlled. Costs were correlated with impairment status (the less controlled, the higher the cost), with the highest costs associated with number of school days lost, medications used, and healthcare utilization. Costs decreased significantly with improved impairment status, with the greatest benefit from fewer overnight hospitalizations (21.6-fold reduction in costs from baseline; P=0.005).

CONCLUSIONS: The economic burden of severe or difficult-to-treat asthma in children increases with increasing impairment, and even mild improvement is associated with reduction in cost. Clinical programs that improve disease management and alleviate the burden of severe or difficult-to-treat asthma are needed.

Funded by Genentech

CMV co-infection with Pneumocystis pneumonia in a newly diagnosed AIDS patient

Brandon Hooks DO, Rami Abboud MD, Mali Ehtesham MD, Sayed Kazmi MD

INTRODUCTION: Cytomegalovirus (CMV) pneumonitis is an infrequent diagnosis seen in AIDS/HIV patients. The exact pathogenesis is not well understood. In case reports available, the extent of disease ranged from minimal interstitial pneumonitis to severe diffuse alveolar damage.

CASE DISCUSSION: A 52-year-old previously well Caucasian male presented with three weeks of progressive dyspnea and hypoxia. Chest radiograph demonstrated bilateral airspace disease. CT Thorax revealed diffuse bilateral interstitial process sparing sub pleural areas. Bronchoscopy with transbronchial biopsy and bronchoalveolar lavage was positive for Pneumocystis pneumonia. Laboratory testing revealed positive HIV antibodies with CD4 count < 5, consistent with acquired immunodeficiency syndrome. Appropriate treatment was initiated with interval improvement. On day 6 of hospitalization, he developed worsening respiratory failure requiring intensive care monitoring. The patient was found to have a unilateral spontaneous pneumothorax requiring chest tube placement. Labs noted elevated CMV titer (2890 IU/mL, 3.46 logIU/mL). Repeat CT thorax showed a 1.4 x 1.2 cm nodule in the left lingula and lymphocytic interstitial pneumonitis features. Open lung biopsy revealed CMV inclusion bodies. Ganciclovir was initiated following which patient had resolution of symptoms.

SUMMARY: CMV pneumonitis is an infrequent condition encountered in AIDS/HIV patients. The majority of CMV infections in HIV patients are viremia and retinitis. CMV titers are not sufficient in establishing the diagnosis requiring histopathologic confirmation. Atypical chest radiograph and CT scan imaging consistent with interstitial process should raise suspicion for opportunistic infections such as CMV.

Hypereosinophillic Syndrome, a complex medical diagnosis

Brandon Hooks DO, Mali Ehtesham MD, Sayed Kazmi MD

INTRODUCTION: Hypereosinophillic syndrome (HES) is a rare condition characterized by peripheral blood eosinophilia with manifestations of organ system involvement or dysfunction directly related to eosinophilia in the absence of parasitic, allergic, or other causes. Any organ may be involved. Cardiac involvement is particularly fatal.

CASE DISCUSSION: A 63-year-old Caucasian male presented with exertional dyspnea and lower extremity weakness for one week. CT/Thorax demonstrated bilateral pleural effusions with subcutaneous edema in the thorax and abdomen. Total creatinine phosphokinase level was 3,227 units/L and aldolase 136.3 units/L. Laboratory testing revealed a white blood cell count 20.31 K/mcL, eosinophil count 3.59 K/mcL, and 16% eosinophils. Physical exam was significant for conversational dyspnea, diminished breath sounds, harsh 3/6 systolic ejection murmur at the apex, and proximal lower extremity weakness. Echocardiogram revealed left ventricular hypertrophy with hyperdynamic systolic function and obstruction. Pleural fluid analysis revealed 26% eosinophils. Bone marrow biopsy demonstrated hypercellular bone marrow (60-70%) with increased eosinophilic precursors. Skeletal muscle biopsy demonstrated eosinophilia-associated myopathy. Infectious work up was negative. The patient was started on glucocorticoid treatment resulting in clinical improvement and symptom resolution therefore confirming diagnosis of HES.

SUMMARY: The etiology of HES is not well known and most common in men over age of 50. Diagnosis involves excluding other causes of eosinophilia plus bone marrow and cytogenic tests. The multisystem involvement and infrequency with which the syndrome is encountered, this case demonstrates the challenge in diagnosing HES.

The novel LAMA/LABA co-suspension technology of glycopyrrolate/formoterol fixed-dose combination MDI significantly improves health status in symptomatic patients with COPD

Fernando J Martinez, Leonardo M Fabbri, Gary T Ferguson, Chad Orevillo, Patrick Darken,[4] Colin Reisner

Rationale: The Global initiative for chronic Obstructive Lung Disease (GOLD) therapeutic strategy recommends long acting bronchodilators to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD). Glycopyrrolate/formoterol (GFF) is a novel long-acting muscarinic antagonist/long-acting β_2-agonist (LAMA/LABA) co-suspension fixed-dose combination delivered by metered dose inhaler (MDI). We compared GFF MDI (glycopyrrolate 18 µg/formoterol fumarate 9.6 µg) versus individual components GP MDI (glycopyrrolate 18 µg) and FF MDI (formoterol fumarate 9.6 µg) and placebo MDI on health status assessed with the St George's Respiratory Questionnaire (SGRQ) as a function of baseline severity of symptoms as assessed in patients with moderate-to-very-severe COPD by the COPD Assessment Test (CAT) in two Phase III studies (PINNACLE-1 and -2).

Methods: Data from PINNACLE-1 and -2 were pooled for this analysis. In the two randomized, double-blind, placebo-controlled, parallel-group, multicentre studies, patients received GFF, GP, FF, or placebo, all delivered via co-suspension technology MDI (7:6:6:3) twice-daily for 24 weeks. For these analyses the changes in SGRQ scores were examined as a function of baseline severity of symptoms as assessed by CAT (≥10, ≥15, ≥20).

Results: Overall, 3699 patients were included in the pooled analysis, of whom 3002 (81.2%) completed 24 weeks of treatment, 54.8% were <65 years of age, 55.9% were male, and 90.2% were white. COPD severity based on lung function alone was moderate in 53.1%, severe in 41.7% and very severe in 5.2% of patients. CAT scores were <10 in 12.3%, ≥10 in 87.2%, ≥15 in 69.1%, and ≥20 in 43.9% of patients. The magnitude of benefit observed in SGRQ score with GFF increased compared to placebo and components with increasing baseline CAT scores. In subjects with CAT ≥20 at baseline, the magnitude of benefit of GFF compared to placebo was estimated to exceed the minimal clinically important difference of 4.0 units in SGRQ total score. Similar relationships were observed using responder analyses.

Conclusion: The beneficial effect on health status of a combination LAMA/LABA increases as a function of baseline severity of symptoms. Similarly, the beneficial effect on SGRQ of a combination LAMA/LABA versus the individual components is most evident in patients who are the most symptomatic. These results support consideration of baseline symptom levels when evaluating the magnitude of benefit of LAMA/LABAs.

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Pooled analyses from PINNACLE-1 and -2: the novel LAMA/LABA co-suspension technology glycopyrrolate/formoterol fixed-dose combination delivered by MDI shows improvement versus monocomponents in patients with COPD

Fernando J Martinez, Klaus F Rabe, Roberto Rodriguez-Roisin, Leonardo M Fabbri, Gary T Ferguson, Paul W Jones, Stephen I Rennard, Shahid Siddiqui, Chad Orevillo, Patrick Darken, Colin Reisner

Rationale: GFF MDI is a long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) co-suspension technology of glycopyrrolate 18 µg/formoterol fumarate 9.6 µg fixed-dose combination delivered by a novel metered dose inhaler (MDI). The efficacy and safety of GFF MDI versus monocomponents GP MDI (glycopyrrolate 18 µg) and FF MDI (formoterol fumarate 9.6 µg) were evaluated in two Phase III studies in patients with moderate-to-very-severe COPD (PINNACLE-1 and -2) irrespective of baseline severity (GOLD A, B, C, and D).

Methods: PINNACLE-1 and -2 had similar study designs and patient populations such that data could be pooled to enable aggregate estimation of effects and evaluation of under-powered endpoints. Both were randomized, double-blind, placebo-controlled, parallel-group, multicenter studies, where patients received GFF, GP, FF, or placebo, all delivered using co-suspension technology MDI (7:6:6:3) twice-daily for 24 weeks of treatment. The primary endpoint was change from baseline in morning pre-dose trough forced expiratory volume in 1 second (FEV_1) at 24 weeks.

Results: The pooled analysis included 3699 patients, and 3002 (81.2%) completed 24 weeks' treatment; median age was 63 years (range: 40–80), 55.9% were male, and 90.2% were white. COPD Assessment Test scores were ≥10 in 87.2% of patients. Airflow limitation was mild in 0.1% (GOLD 1), moderate in 53.1% (GOLD 2), severe in 41.7% (GOLD 3) and very severe in 5.2% (GOLD 4) of patients. Pooled data show that GFF demonstrated improvement versus placebo and monocomponents in morning pre-dose trough FEV_1 at 24 weeks ($p<0.0001$). Improvement versus placebo and monocomponents was also observed for peak change in FEV_1 within 2-hours post-dose at Week 24 ($p<0.0001$). Pooled St. George's Respiratory Questionnaire data demonstrated a reduction in total score with GFF at Week 24 versus placebo ($p=0.0051$) and GP ($p<0.0094$). GFF time to first moderate-to-severe exacerbation hazard ratios (95% CI) relative to placebo, GP and FF were 0.736 (0.575, 0.943; $p<0.02$), 0.781 (0.639, 0.955; $p<0.02$) and 0.861 (0.699, 1.06; $p=0.159$). Patients receiving GFF required less relief medication (mean daily number of Ventolin® HFA puffs) over 24 weeks compared to placebo ($p<0.0001$) or GP ($p<0.0001$).

Conclusion: Pooled data from the Phase III PINNACLE-1 and -2 trials in patients with moderate-to-very-severe COPD demonstrated that GFF MDI (glycopyrrolate 18 µg/formoterol fumarate 9.6 µg) provides greater improvements in lung function than its individual monocomponents and placebo. These data further support the efficacy of GFF MDI as a bronchodilator therapy for patients with COPD.

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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)

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Rationale: GFF MDI is a novel LAMA/LABA co-suspension technology (glycopyrrolate 18 µg/formoterol fumarate 9.6 µg) 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 µg) and FF MDI (formoterol fumarate 9.6 µg 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 µg 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 [FEV_1]). 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 FEV_1 and peak FEV_1 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.

Conclusions: Overall, the results of PINNACLE-3, the 28-week extension study to two Phase III studies demonstrated long-term safety, tolerability, and consistent and sustained efficacy, of GFF MDI (glycopyrrolate/formoterol 18/9.6 µg) twice-daily compared with its monocomponents in patients with moderate-to-very-severe COPD over 52 weeks of treatment.

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24-hour lung function profile of novel co-suspension technology glycopyrrolate/formoterol metered dose inhaler versus placebo and Spiriva® Respimat®, in patients with moderate-to-very-severe chronic obstructive pulmonary disease

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Rationale: Glycopyrrolate 18 µg/formoterol fumarate 9.6 µg metered dose inhaler (GFF MDI) is a novel LAMA/LABA co-suspension technology inhaler administered twice daily (BID). We report a 4-week Phase IIIb study to determine the 24-hour lung function profile of GFF MDI relative to placebo and open-label Spiriva® Respimat® in patients with moderate-to-very-severe chronic obstructive pulmonary disease (COPD), in particular to characterize the lung function profile following the evening GFF MDI dose through to the next morning.

Methods: In this randomized, three-period, three-treatment, double-blind, multi-center, crossover trial, patients received 4 weeks' treatment with GFF MDI BID, placebo MDI BID and once-daily (QD) Spiriva® Respimat® 5 µg with 7-21 day washouts. Pulmonary function testing was performed on Day 1 of each treatment period and over 24 hours on Day 29. The primary efficacy endpoint was normalized and baseline-adjusted forced expiratory volume in one second (FEV_1) area under the curve from 0 to 24 hours (AUC_{0-24}) on Day 29. Secondary endpoints included changes in FEV_1, and inspiratory capacity (IC). Safety was also assessed.

Results: The modified intent-to-treat population comprised 75 patients (mean [range] age 62 (40-79) years, 64% female, 63% smokers). For the primary endpoint, FEV_1AUC_{0-24} on Day 29, GFF MDI showed a statistically significant least squares mean (LSM) difference from placebo ($p<0.0001$) and Spiriva® Respimat® ($p=0.0001$). On Day 29, GFF MDI LSM difference from placebo in FEV_1AUC was similar for hours 12-24 and 0-12; GFF MDI LSM difference versus Spiriva® Respimat® was greater during hours 12-24 ($p<0.0001$) than hours 0-12 ($p=0.0325$). On Day 29, morning post-dose peak FEV_1 change from baseline LSM difference was 278 mL versus placebo (95%CI: 225, 330; $p<0.0001$), and 81 mL versus Spiriva® Respimat® (95%CI: 29, 133; $p=0.0026$); evening values were 337 mL (95%CI: 282, 392; $p<0.0001$) and 165 mL (95%CI: 110, 219; $p<0.0001$), respectively. LSM differences in peak IC change from baseline following morning and evening doses on Day 29 were statistically significant versus placebo (both $p<0.0001$) and Spiriva® Respimat® ($p=0.03$ and $p=0.004$, respectively). There were no significant safety/tolerability findings.

Conclusions: GFF MDI significantly improved 24-hour lung function versus placebo in moderate-to-very-severe COPD, with a consistent benefit observed following morning and evening dosing. A significant improvement versus Spiriva® Respimat® QD was observed in the first 12-hours of dosing, with a larger effect observed in the second 12-hours of dosing based on FEV_1AUC,

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A Randomized, Multi-Center, Single Visit Study to Compare Feno Measured with the Niox Mino and the Niox Vero in Subjects with Asthma

Kathy Rickard

Rationale: Measurement of exhaled Nitric Oxide (FeNO) is useful in the diagnosis and management of asthma. The primary objective of this study was to assess the agreement and repeatability of FeNO measured with NIOX MINO and NIOX VERO.

Methods: Data from two randomized, multi-center, single visit studies were pooled. All Subjects performed two measurements with the NIOX MINO and the NIOX VERO in random order. The primary endpoint was the proportion of subjects with FeNO values within the tolerance limits. The secondary endpoint was to evaluate the agreement of FeNO measured with NIOX MINO and the NIOX VERO.

Results: 109 completed one valid FeNO measurement on each device. 90.8%(99/109) of the subjects were within the tolerance limits for the first valid FeNO measurement. The mean observed paired difference for the first valid FeNO measurement on each device was -4.6 ppb (95% CI: -5.825 to -3.3//; $p<0.0001$). Weighted Deming Regression Analysis showed slope of 0.842 (95% CI: 0.757, 0.927) and Yintercept of -0.472 (95% CI: -1.999, 1.055). Paired differences were centered close to 0. Intra-subject repeatability of NIOX VERO was significantly better than NIOX MINO ($p= 0.0112$).

Conclusions: FeNO measurements using the NIOX VERO were slightly lower than on the NIOX MINO, however, no substantial differences were noted between replicates within age groups, gender groups or randomization sequences and the difference is within the technical specifications of the device. The results support a high degree of intra-subject repeatability. The same agreement was seen when comparing the first valid measurement and the mean of the two measurements.

Funded by Circassia

FEV_1 Improvement with Dupilumab by Different Baseline Patient Characteristics in Patients with Uncontrolled Persistent Asthma

Jonathan Corren, MD, Sheldon Spector, MD, Bingzhi Zhang, PhD, Gianluca Pirozzi, MD, PhD, Heribert Staudinger, MD, PhD, Robert R. Evans, PharmD, Neil M.H. Graham, MD, Mariana Louis-Tisserand, MD, Ariel Teper, MD

Introduction: Dupilumab improves forced expiratory volume in 1 second (FEV_1) and reduces severe exacerbation rates in adults (≥18 years) with uncontrolled persistent asthma on medium-to-high dose inhaled corticosteroids plus a long-acting beta-agonist (NCT01854047). We report the effect of dupilumab on FEV_1 according to baseline patient characteristics.

Methods: Patients were randomized to 24-weeks add-on therapy with dupilumab, 200 or 300 mg every 2 weeks (q2w) or every 4 weeks, or placebo. Least-squares (LS) mean change from baseline at Week 12 in FEV_1 (L) and LS mean difference from placebo were evaluated for the population receiving q2w dupilumab vs placebo, according to: race, body mass index (BMI), smoking history (>10 pack-years), FEV_1 % predicted, 5-item asthma control questionnaires (ACQ-5), and number of severe exacerbations rates in the year prior to study. Adverse events (AEs) and lab assessments were evaluated.

Results: FEV_1 improved in all subgroups at Week 12 vs placebo. Race, BMI, FEV_1 % predicted, ACQ-5 score, smoking history had no effect on the relative efficacy of dupilumab in improving FEV_1. Patients with ≥1 vs 1 exacerbation in the prior year experienced a significantly greater increase in FEV_1 with dupilumab. AEs were similar across treatment groups (dupilumab 78-80%; placebo 75%) with the most commonly occurring in dupilumab-treated patients being upper respiratory tract infection (dupilumab 13-15%; placebo 18%) and injection-site erythema (dupilumab 14-22%; placebo 8%).

Conclusions: Across a variety of subgroups in patients with uncontrolled persistent asthma, lung function improved when dupilumab was added to standard therapy. Dupilumab had an acceptable safety profile.

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Dupilumab Improves Lung Function Inclusive of Small Airways in Patients with Uncontrolled Persistent Asthma: Results From a Phase 2b Clinical Trial

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Introduction: Dupilumab improves forced expiratory volume in 1 second (FEV_1) and reduces severe exacerbations in adults (age ≥18 years) with uncontrolled persistent asthma on medium-to-high dose inhaled corticosteroids plus a long-acting beta-agonist (ICS/LABA) (NCT01854047). We report the effects of dupilumab on a range of lung-function measures.

Methods: Patients were randomized to 24 weeks of add-on therapy with dupilumab 200mg or 300mg every 2 (q2w) or 4 weeks, or placebo. Lung function was assessed after 2 and 4 weeks, then every 4 weeks during the treatment period along with FEV_1, forced vital capacity (FVC), and forced expiratory flow of 25–75% of FVC (FEF25–75%). Peak expiratory flows in the morning (AM PEF) and evening (PM PEF) were collected daily. FEV_1, AM/PM PEF are prespecified endpoints; FVC and FEF25-75% are post-hoc analyses. Adverse events (AEs) and lab assessments were evaluated. We report results at baseline, Week 12, and Week 24 for the q2w groups.

Results: Dupilumab significantly improved FEV_1, AM/PM PEF, FVC, and FEF25–75% at Weeks 12 and 24 vs placebo ($P<0.05$ in both dose groups). AEs were similar across treatment groups (dupilumab 78-80%; placebo 75%) with the most commonly occurring in dupilumab-treated patients being upper respiratory tract infection (dupilumab 13-15%; placebo 18%) and injection-site erythema (dupilumab 14-22%; placebo 8%).

Conclusions: Dupilumab administered q2w as add-on to ICS/LABA therapy was associated with significant improvements across a range of lung-function measures, suggesting that the observed improvements were in both the large and the small airways. Dupilumab had an acceptable safety profile.

Funded by Sanofi and Regeneron Pharmaceuticals, Inc.

Effect of Dupilumab on FEV_1 and Severe Exacerbations in Patients with Uncontrolled Persistent Asthma: A Subgroup Analysis Defined According to Early-Onset and Late-Onset Asthma

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Introduction: Dupilumab improves forced expiratory volume in 1 second (FEV_1) and reduces severe exacerbations in adults (≥18 years) with uncontrolled persistent asthma on medium-to-high dose inhaled corticosteroids plus a long-acting beta-agonist (ICS/LABA) (NCT01854047). This analysis reports the effects of dupilumab according to age of asthma onset.

Methods: Patients were randomized to 24 weeks add-on therapy with dupilumab 200 or 300mg every 2 (q2w) or 4 weeks, or placebo. Least-squares (LS) mean change from baseline in FEV_1 (L) at Week 12 was evaluated according to early (≤40 years) and late-onset (>40 years) asthma for patients receiving the q2w doses, q2w doses pooled, or placebo. The annualized rate of severe exacerbation events was calculated at 24 weeks. Adverse events (AEs) and lab assessments were evaluated.

Results: FEV_1 was significantly improved in patients with early-onset asthma (n=96 and 109; dupilumab 200mg and 300mg q2w, respectively; $P<0.01$ for both doses vs placebo), with a similar trend for late-onset asthma (n=40 and 37; dupilumab 200mg [$P=0.0067$] and 300mg q2w [$P=0.0608$]); FEV_1 was significantly improved in both pooled subgroups ($P<0.001$ vs placebo). Severe exacerbations were lower with both dupilumab doses vs placebo in patients with early-onset asthma (both $P<0.05$), with a similar trend for late-onset asthma; severe exacerbations were reduced in both pooled subgroups ($P<0.05$). Most common AEs were upper respiratory tract infection (dupilumab 13-15%; placebo 18%) and injection-site erythema (dupilumab 14-22%; placebo 8%).

Conclusions: Dupilumab q2w improved FEV_1 and reduced severe exacerbations in patients with early- or late-onset asthma. Dupilumab had an acceptable safety profile.

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