Eastern Pulmonary Conference
August 31-September 3, 2017 ~ Palm Beach, FL

All Scientific Posters will be on display in Ponce de Leon 5 & 6 beginning Friday morning, September 1st. 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

Asthma Always on My Mind: Findings from a Patient Survey of Negative Impact on Asthma Quality of Life

Maureen George, PhD; Melanie Carver; Sanaz Eftekhari; Deidre Washington, PhD

Introduction: Asthma can have an emotional, social and economic impact on patients—and this burden is often higher among patients with severe and uncontrolled asthma. The My Life With Asthma Survey was conducted to better understand and qualify patient perceptions of and experience with severe and uncontrolled asthma.

Methods: Between February 27, 2017 and April 8, 2017, the Asthma and Allergy Foundation of America (AAFA) invited adults with asthma to participate in an online, cross-sectional survey. After pre-testing, the survey was sent to over 200,000 individuals in AAFA's e-mail database, registered patient community, and social networks.

Results: A total of 804 individuals responded of which 185 were classified as "severe and uncontrolled" by report of symptoms. Seventy-eight percent of the severe group said their asthma was "always in the back of their mind" (vs. 47% of the not severe group). Regression analysis demonstrated that patients who always thought about asthma were 5.86 times more likely to experience negative impact on asthma quality of life (AQoL) than patients who reported "Never" thinking about asthma. Further, 76% of the severe group reported feeling frustrated by their asthma; patients who felt "Frustrated by asthma" were 30.93 times more likely to experience negative impact on AQoL compared to those who did not report frustration.

Conclusions: The respondents with severe and uncontrolled asthma experienced significantly more frequent thoughts of, and frustration with, asthma. This group is important to target with support and interventions as these experiences were significantly more likely to result in negative impact to quality of life.

Funding: The survey was supported by AstraZeneca

Early Decreases in Blood Eosinophil Levels with Reslizumab

Pascal Chanez, Mirna McDonald, Margaret Garin, Kevin Murphy

Introduction: In clinical trials, the anti-interleukin-5 monoclonal antibody reslizumab reduced blood eosinophil levels, reduced asthma exacerbations, and improved lung function and asthma control as early as 4 weeks after the first dose. Assessment of changes in eosinophils earlier than this has not been reported.

Methods: Data were pooled from subgroups of patients with early samples (day 2–3 and week 2–3) in two phase 3 BREATH trials in asthma patients aged 12–75 years, with a screening blood eosinophil count ≥400/µL, receiving either intravenous reslizumab (3.0mg/kg) or placebo every 4 weeks.

Results: Early blood samples were taken from 151 patients (placebo: 74, reslizumab: 77) in the two studies. Median serum reslizumab concentrations were zero at baseline and 46400, 20600, 13550, 19300, 21000, and 23300ng/mL at day 2–3, week 2–3, week 4, week 8, week 12, and week 16, respectively (week 4–16 samples were all pre-dose). Mean blood eosinophil levels for placebo- and reslizumab-treated groups were 591 and 702/µL at baseline, 584 and 184/µL at day 2–3, 563 and 138/µL at week 2–3, 518 and 134/µL at week 4, 545 and 113/µL at week 8, 535 and 96/µL at week 12, and 481 and 51/µL at week 16, respectively.

Conclusion: Substantial decreases in blood eosinophil levels were detected as early as 2–3 days after the first dose of reslizumab in patients with severe asthma and elevated blood eosinophil levels at baseline. Blood eosinophil levels remain low but detectable throughout 16 weeks of reslizumab doses.

Funding: Teva

Efficacy of Reslizumab in Asthma Patients Eligible for Omalizumab Treatment

Marc Humbert, Mario Castro, Mirna McDonald, Matthew Germinaro

Introduction: In patients with inadequately controlled asthma and elevated blood eosinophils, intravenous reslizumab significantly reduced exacerbation frequency and consistently improved lung function. Many patients with eosinophilic asthma also have atopy. This post-hoc analysis was conducted to assess the efficacy of reslizumab among patients who would have been eligible for omalizumab treatment.

Methods: The phase 3 BREATH study 3082 enrolled 489 inadequately controlled asthma patients, 12–75 years of age, receiving medium-to-high dose inhaled corticosteroid ± additional controller(s), with ≥1 exacerbation(s) in the previous year, and screening blood eosinophils ≥400/µL. Baseline assessments included total and specific immunoglobulin E (IgE) levels, atopy status, and body weight to determine eligibility for treatment with omalizumab according to the US label. Concomitant omalizumab treatment was prohibited during the study. Negative binomial regression model was utilized to estimate the frequency of clinical asthma exacerbations with reslizumab versus placebo.

Results: 464 patients had complete data for omalizumab eligibility assessment, of whom 31% (146/464) were eligible for omalizumab treatment according to the US label (i.e. total IgE 30–700 IU/mL, body weight <150kg and perennial allergen sensitization). Intravenous reslizumab resulted in reductions in the annualized rate of exacerbations compared with placebo in patients eligible for omalizumab (n=146; rate ratio 0.58; 95% CI 0.36–0.95).

Conclusions: In patients with inadequately controlled asthma and elevated blood eosinophils, a 42% reduction in exacerbation rates was seen with reslizumab in the omalizumab-eligible patient population, indicative of the clinically meaningful benefit of reslizumab in patients eligible for treatment with either biologic.

Funding: Teva

Efficacy of Reslizumab in Asthma Patients with Aspirin Sensitivity and Elevated Blood Eosinophils

Rohit Katial, Flavia Hoyte, Mirna McDonald, Matthew Germinaro

Introduction: Aspirin Exacerbated Respiratory Disease (AERD) consists of chronic rhinosinusitis with nasal polyps (CRSwNP), severe asthma, and intolerance to aspirin (ASA) and other NSAIDs. Eosinophilic inflammation plays an important role in AERD. Our aim was to determine the effect of IV reslizumab on clinical asthma exacerbations (CAE) in patients with inadequately controlled asthma and historical ASA sensitivity.

Methods: The methodology and outcomes of studies 3082 and 3083 have been previously reported (Castro M, et al. Lancet Resp Med 2015). Patients with asthma and elevated blood eosinophils (≥400cells/µL) who remained inadequately controlled despite standard-of-care therapy were randomized to placebo or reslizumab (3mg/kg [IV] Q4W) for 52 weeks. In this analysis, pooled results assessed change in CAE frequency for patients with ASA sensitivity.

Results: 11% (n=103/953) of patients had historical ASA sensitivity. Data for concurrent sinus disease were not available for the entire group, but 56 of these patients (6%) were known to also have CRSwNP. Patients with ASA sensitivity who received IV reslizumab (n=48) had a 62% reduction in the annual rate of CAE versus placebo (RR 0.38 [95% CI 0.21, 0.70]). Patients with ASA sensitivity and known CRSwNP who received reslizumab (n=28) had a 79% reduction in the annual rate of CAE versus placebo (RR 0.21 [95% CI 0.08, 0.58]). Both groups achieved clinically meaningful improvements in forced expiratory volume in 1 second.

Conclusions: Patients with inadequately controlled asthma, elevated blood eosinophils, and ASA sensitivity (±CRSwNP) received significant therapeutic benefit, further supporting the use of reslizumab in this clinical setting.

Funding: Teva

Asthma Exacerbations and Lung Function Decline in a Pooled Analysis of Adolescents and Adults From Randomized Controlled Trials of Omalizumab

William W. Busse, Bradley E. Chipps, Karin Rosén, Benjamin Ortiz, Tmirah Haselkorn, Benjamin L. Trzaskoma, Bobby Q. Lanier, Stanley J. Szefler

Rationale: The impact of asthma exacerbations on lung function decline was examined in a post hoc analysis of children enrolled in a 52-week controlled trial of omalizumab. Preliminary findings suggested that omalizumab may confer a protective effect on lung function in children experiencing exacerbations. We sought to extend these findings in a pooled analysis of adolescents and adults from two randomized controlled trials of omalizumab.

Methods: Data were pooled from two randomized trials of omalizumab that included patients 12–75 years of age: 1) EXTRA, a 48-week prospective, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of patients with inadequately controlled severe asthma despite high-dose inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA), 2) INNOVATE, a 28-week, randomized, parallel-group, placebo-controlled, multicenter study of patients with asthma inadequately controlled despite high-dose ICS and LABA with reduced lung function and recent severe exacerbations. Asthma exacerbations were defined as an exacerbation lasting ≥3 days and requiring treatment with systemic steroids. Exacerbators were defined as those patients who experienced ≥ 1 exacerbation during the study. Changes in percent predicted pre-bronchodilator FEV_1 ($ppFEV_1$) from baseline to Weeks 4, 12, 20, and 28 by treatment (omalizumab/placebo) and exacerbation status (exacerbators/non-exacerbators during the study period) were examined. P-values were calculated using two-sample t-tests from ANOVA.

Results: A total of 1090 adolescents and adults were included in this analysis (omalizumab exacerbators: n=199, placebo exacerbators: n=241, omalizumab non-exacerbators: n=349, placebo non-exacerbators: n=301). Baseline patient characteristics in the pooled population were generally similar with a population that was mostly female, white, and had an average age of ~44 years. Baseline mean (SD) $ppFEV_1$ was lower in the omalizumab exacerbators (61.5 [14.8]) and placebo exacerbators (61.5[14.5]) than omalizumab non-exacerbators (65.2[15.1]) and placebo non-exacerbators (64.8[13.5]). Omalizumab exacerbators showed greater improvement in ppFEV1 at Week 12 and maintained this improvement in $ppFEV_1$ compared with placebo exacerbators through Week 28, with lung function values similar to omalizumab non-exacerbators. Omalizumab non-exacerbators demonstrated statistically significant improvement in $ppFEV_1$ at Week 12 compared with placebo non-exacerbators, which was maintained through the end of Week 28.

Conclusion: This large post hoc analysis of data from the EXTRA and INNOVATE clinical studies extends prior findings in children and suggests that treatment with omalizumab may provide a protective effect on lung function in adolescents and adults who experience asthma exacerbations.

Funding: 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 FEV_1 percentage predicted was 88% (17) and improved on average by 8% to 95% (20), which represents an absolute improvement of 160mLs 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/ □L with 54.5% of patients having eosinophils
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 (SD) eosinophils decreased by 34% to 209 (151) cells/ □L.

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.

Funding: Genentech

Real-World Practice Patterns for Prevention and Management of Potential Side Effects of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Wencel ML, Haselkorn T, Limb SL, Stauffer J, Trzaskoma B, Raimundo K, LaCamera P

Introduction: Pirfenidone is an oral anti-fibrotic agent approved for idiopathic pulmonary fibrosis (IPF). Real-world data on side effect management for pirfenidone are limited. Strategies for managing potential anti-fibrotic therapy side effects were examined in a diverse sample of U.S. pulmonologists.

Methods: An online, self-administered survey was fielded to pulmonologists between April 10-May 17, 2017. Pulmonologists were included if they spent >20% of their time in direct patient care and had ≥10 patients with IPF on anti-fibrotic therapy. Participants answered questions regarding initiating pirfenidone, dose titration, and management of potential side effects.

Results: A total of 169 pulmonologists participated. Gastrointestinal intolerance (GI) was the most important factor for implementing alternative titration schedules for pirfenidone. Approximately three-quarters recommend the standard titration scheme to start, however, a range of titration schedules up to 8 weeks were described, with a 4-week schedule being common (1 capsule three times/day (TID) for two weeks, 2 capsules TID for two weeks, then 3 capsules TID). Pulmonologists reported that the majority of patients treated with an alternative titration schedule were able to achieve full dose of pirfenidone. Pulmonologists who reported being most effective at mitigating pirfenidone-related GI side effects by dosing at mealtimes were more likely to recommend taking pirfenidone during a substantial meal than pulmonologists who reported being less effective.

Conclusions: Pulmonologists report that alternative titration schedules for initiating pirfenidone are common and can aid in achieving the full dose in patients. Strategies to ameliorate pirfenidone-related GI side effects include taking pirfenidone during a substantial meal.

Funding: Genentech

Effect of Pirfenidone on a Novel Definition of Progression-Free Survival (PFS) in Patients With Idiopathic Pulmonary Fibrosis (IPF): Pooled Analysis From Phase III Trials

David Lederer, Ben Trzaskoma, Klaus-Uwe Kirchgässler, Michael Kreuter, Jeffrey Swigris

Introduction: No consensus exists regarding the definition of PFS in IPF as a potential composite endpoint for clinical trials or consideration by regulatory authorities. Respiratory-related hospitalizations have been identified as a significant negative prognostic factor in IPF and proposed as a component of future PFS definitions. This analysis compared the effect of pirfenidone on PFS using a pre-specified PFS definition (with 6-minute walk distance [6MWD], forced vital capacity [FVC] or death) vs a novel definition using respiratory-related hospitalizations in lieu of 6MWD.

Methods: Pooled data from patients randomized to pirfenidone 2403 mg/day or placebo in ASCEND or CAPACITY (N=1247) for up to 12 months were used. The pre-specified PFS definition was time to first occurrence of ≥10% absolute FVC decline from baseline, ≥50-m 6MWD decrease or death. The alternative PFS definition was time to first occurrence of a respiratory-related hospitalization, ≥10% absolute FVC decline from baseline or death. Time-to-first-event analyses using both PFS definitions were performed. Hazard ratios (HRs) were based on Cox models. Descriptive statistics compared the relative contribution of the 3 components for each definition with the first qualifying event as well as the total number of events.

Results: The novel PFS definition had a lower total number of qualifying events in the pirfenidone and placebo groups vs the pre-specified definition (alternative definition: 14.4% pirfenidone vs 27.4% placebo; pre-specified definition: 26.6% pirfenidone vs 39.4% placebo). The proportion of patients with a first qualifying event of respiratory-related hospitalization was 5.5% with pirfenidone vs 10.1% with placebo. The novel PFS definition favored pirfenidone (HR, 0.49; 95% CI, 0.38, 0.64; $P<0.0001$) vs the pre-specified definition (HR, 0.62; 95% CI, 0.51, 0.75; $P<0.0001$), indicating a greater relative risk reduction with pirfenidone compared with placebo.

Conclusions: The novel PFS definition, despite having a lower event rate over 12 months, was at least as discriminating as the pre-specified definition for estimating the pirfenidone treatment effect.

Funding: F. Hoffmann-La Roche, Ltd./Genentech, Inc.

Effect of Pirfenidone on Breathlessness as Measured by the UCSD-SOBQ Score in Patients With Idiopathic Pulmonary Fibrosis (IPF) With Moderate Lung Function Impairment

Marilyn K. Glassberg, Marlies Wijsenbeek, Frank Gilberg, Klaus-Uwe Kirchgässler, Carlo Albera

Rationale: Treatment of IPF with pirfenidone slows disease progression as measured by changes in forced vital capacity (FVC), independent of baseline FVC values. In a previous analysis of patients with limited vs more advanced lung function impairment, increases in University of California, San Diego Shortness of Breath Questionnaire (UCSD-SOBQ) scores were more pronounced in patients with GAP stage II/III vs GAP stage I and in patients with baseline percent predicted forced vital capacity (%FVC) <80% vs %FVC ≥80%. This study further examined the effect of pirfenidone on UCSD-SOBQ in these subpopulations.

Methods: Patients randomized to pirfenidone 2403 mg/day or placebo in ASCEND or CAPACITY (N=1247) were stratified by GAP stage I (252 pirfenidone, 241 placebo) vs GAP stage II/III (371 pirfenidone, 383 placebo) and by %FVC ≥80% (146 pirfenidone; 170 placebo) vs <80% (477 pirfenidone; 454 placebo). Categorical and continuous changes from baseline in UCSD-SOBQ scores were assessed over 12 months and compared between treatment groups using the Wilcoxon rank-sum test.

Results: Among patients receiving pirfenidone, those with GAP stage II/III had higher UCSD-SOBQ scores after 12 months than those with GAP stage I (median increase: 9.4 vs 5.0); similar results were observed with placebo (12.5 vs 4.3). In patients with GAP stage II/III, the median UCSD-SOBQ score increase at 12 months for pirfenidone was 9.4 vs 12.5 for placebo (median difference, −3.5; 95% CI, −6.2, −0.5; *P*=0.0161). Pirfenidone reduced the proportion of patients with UCSD-SOBQ score increases of >15 points (38.4% vs 45.6%; *P*=0.0449) and >20 points (28.6% vs 37.7%; *P*=0.0089) at 12 months compared with placebo. Results in patients with %FVC ≤80% were comparable to GAP stage II/III.

Conclusions: In patients with IPF with moderate lung function impairment, pirfenidone reduced the progression of breathlessness compared with placebo. Patients receiving pirfenidone showed less change from baseline in UCSD-SOBQ score, and a lower proportion of patients had more pronounced increases in UCSD-SOBQ scores at 12 months.

Funding: F. Hoffmann-La Roche Ltd./Genentech, Inc.

Testing Leading to the Diagnosis of Idiopathic Pulmonary Fibrosis in Medicare Patients

Joshua Mooney, Eunice Chang, Sheila R. Reddy, Jessie T. Yan, Michael S. Broder

Rationale. Establishing an accurate diagnosis of idiopathic pulmonary fibrosis (IPF) is a challenging and complicated process with patients often receiving many diagnostic tests before confirming a definitive diagnosis. This study described the current patterns of diagnostic tests used in Medicare patients prior to receiving a claim-based IPF diagnosis.

Methods. This retrospective analysis of the entire Medicare Research Identifiable File included newly diagnosed IPF patients who had ≥5 years of Medicare continuous enrollment before diagnosis. Year 2012 was the index year for diagnosis: a new IPF case was defined as ≥1 inpatient or ≥2 outpatient claims in 2012 with IPF as a listed diagnosis, no claim for other interstitial lung diseases (ILDs) after the last IPF claim and no IPF diagnosis in the 5 years prior to 2012. Use of various diagnostic tests was assessed over a five-year period prior to the first IPF claim diagnosis using descriptive statistics.

Results. 9,504 Medicare patients were included. Mean (SD) age was 81.2 (6.4) years and 49.5% were female. 99.7% had ≥1 test of interest in the 5 years up to and including the diagnosis date. Chest X-rays were most common (98.8%), followed by chest computed tomography (CT) scans (76.9%), pulmonary function tests (PFTs; 67.9%), oxygen saturation (47.1%) and anti-nuclear antibodies (36.2%). Only 14.7% of patients had a chest CT ≥4 years prior to diagnosis, increasing to 25% ≥3 years prior. Not all patients receiving a claims-based IPF diagnosis received the minimum needed testing prior to their diagnosis (HRCT and/or surgical lung biopsy).

Conclusions. In this study, many tests relevant to diagnosing IPF were performed in the 5 years prior to diagnosis, whether for suspicion of ILD or investigation of comorbid conditions. Further, the performance of CT and PFTs with increasing frequency over time suggests an opportunity for earlier diagnosis. Due to the limitations of the database, symptoms could not be captured and it is possible that not all patients identified in fact have the condition.

Funding: F. Hoffmann-La Roche Ltd./Genentech, Inc.

Lung Function Characteristics in the TENOR II Cohort of Difficult-to-Treat Asthma Patients

Eugene R. Bleecker, Robert S. Zeiger, Bradley E. Chipps, Aimee Foreman, Stanley J. Szefler

Introduction: TENOR-II evaluated long-term outcomes (>10 years follow-up) in patients with severe/ difficult-to-treat asthma from TENOR-I. This analysis describes clinical characteristics of TENOR-II patients according to lung function quartile.

Methods: A total of 341 TENOR-I patients were enrolled in TENOR-II and assigned to quartiles (Q) according to their pre-bronchodilator % predicted forced expiratory volume in 1 second ($ppFEV_1$): Q1 (n=84), 19.1%–<60.1%; Q2 (n=86), 60.1%–<72.8%, Q3 (n=85), 72.8%–<87.3% and Q4 (n=84), 87.3%–138.8%. Very poorly controlled (VPC) asthma was defined using NHLBI guidelines. Persistent VPC was defined as VPC at TENOR-I and -II enrollment.

Results: Q1 patients were older (mean years [SD]: 61.1 [12.8]) than those in Q2–4 (59.0 [13.8], 55.2 [17.7] and 55.9 [19.4] respectively). Total IgE geometric means [IU/ml 95% CI] were higher in Q1 patients (87.3 [61.6, 123.8]) than in Q2-Q4 (80.4 [53.4, 121.0], 64.9 [41.9, 100.7] and 57.9 [33.8, 99.3] respectively). Combined inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) use was highest in Q1 (82.1%) compared with Q2 (77.4%), Q3 (59.5%) and Q4 (63.4%). More Q1 patients (38.1%) exacerbated in the previous 3 months than Q2-4 (27.9%, 23.5% and 13.1% respectively). More Q1 patients (94.0%) had persistent VPC asthma than Quartiles 2–4 (37.5%, 30.9% and 28.9% respectively).

Conclusion: Nearly all patients with the poorest lung function in TENOR-II had higher IgE, persistent VPC and increased exacerbation risk compared to patients with higher lung function, despite increased ICS/LABA use in this subgroup. This suggests the need to step-up therapy and more active management for these patients.

Funding: Novartis

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±308.0 days. For patients with treatment augmentation, the mean time from long-acting bronchodilator monotherapy initiation to therapy augmentation was 177.7±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±$4,063.09 and $2,402.11±$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.

Funding: AstraZeneca, LP.

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

Fernando J Martinez, Leonardo M Fabbri, Gary T Ferguson, Chad Orevillo, Patrick Darken, Ubaldo Martin, Colin Reisner

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 µg (equivalent to glycopyrronium/formoterol fumarate dihydrate 14.4/10 µg), GP MDI 18 µg, FF MDI 9.6 µg, 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.

Funding: AstraZeneca, LP

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

Klaus F. Rabe, Fernando J. Martinez, Roberto Rodriguez-Roisin, Leonardo M. Fabbri, Gary T. Ferguson, Chad Orevillo, Patrick Darken, Andrea Maes, Ubaldo J. Martin, and Colin Reisner

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 (FEV_1); 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 FEV_1 or SGRQ event observed on two consecutive visits or on ≥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.

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The Efficacy and Safety of Benralizumab for Treatment of Severe Uncontrolled Eosinophilic Asthma: Overview of the Ongoing WINDWARD Phase III Trial Program

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Introduction: Benralizumab, a humanized, afucosylated, anti-interleukin-5 receptor α monoclonal antibody, induces eosinophil depletion and is being evaluated for treatment of severe, uncontrolled asthma with an eosinophilic phenotype. The WINDWARD program comprises 6 phase 3 trials: SIROCCO, CALIMA, ZONDA, BISE, BORA and GREGALE. Here we summarize primary analysis population data from 3 published studies.

Methods: SIROCCO[1] (N=1,205 randomized) and CALIMA[2] (N=1,306 randomized) were randomized controlled studies of benralizumab 30mg, every 4 or 8 weeks, added to inhaled corticosteroids plus long-acting β_2-agonists (ICS+LABA). Results were stratified 2:1 by baseline blood eosinophils (BES) ≥300 (primary population) versus <300 cells/µL. ZONDA[3] (N=220 randomized) was a randomized controlled study evaluating the oral corticosteroid (OCS)-sparing effect of benralizumab in patients with severe eosinophilic asthma receiving high-dosage ICS+LABA and OCS with BES ≥150 cells/µL.

Results: In SIROCCO, benralizumab significantly reduced annual asthma exacerbation rates (AERs) over 48 weeks versus placebo (rate ratios Q4W: 0.55; 95%CI, 0.42-0.71; p<0.0001; Q8W: 0.49; 95%CI, 0.37-0.64; p<0.0001). In CALIMA, benralizumab significantly reduced annual AERs over 56 weeks versus placebo (rate ratios Q4W: 0.64; 95%CI, 0.49-0.85; p=0.0018; Q8W: 0.72; 95%CI, 0.54-0.95; p=0.0188). Lung function and asthma symptoms improved in both studies. In ZONDA, median OCS dosage reduction from baseline to Week 28 with maintained asthma control was 75.0% for benralizumab (both Q4W and Q8W) versus 25.0% for placebo (p<0.001). The overall frequency and nature of adverse events with benralizumab in these studies were similar to those with placebo.

Conclusions: These studies confirm efficacy and safety of benralizumab for treatment of severe eosinophilic asthma.

Funding: AstraZeneca

Tiotropium Respimat® 2.5 µg Add-on to ICS or ICS+controller medications Improves Lung Function in Adults and Adolescents with Mild, Moderate, or Severe Symptomatic Asthma

William E. Berger, Eli O. Meltzer, Anna Unseld, Asif Shaikh, and Michael Engel

Introduction: The study investigated lung function in adults and adolescents (12–17 years old) taking tiotropium Respimat® (TioR) 2.5µg+inhaled corticosteroids (ICS) or ICS+controller medications.

Methods: Patients with mild, moderate, or severe asthma (≥3 months asthma history; pre-bronchodilator forced expiratory volume [FEV_1] 60–90% of predicted normal); added once-daily TioR (2.5µg or 5µg [2 puffs of 1.25µg or 2.5µg, respectively]; only TioR 2.5µg discussed in this abstract) in the evening or placebo Respimat® (pboR) to ICS or ICS+controller medications in 5 phase III RCTs. In 4 trials, patients received TioR/placebo+ICS: GraziaTinA-asthma® (NCT01316380; 12 weeks; n=464 adults; mild asthma), 2 replicate MezzoTinA-asthma® (NCT01172808/NCT01172821; 24 weeks; n=2100 adults; moderate asthma), and RubaTinA-asthma® (NCT01257230; 48 weeks; n=397 adolescents; moderate asthma). In 1 trial patients received TioR/placebo+ICS+controller medications: PensieTinA-asthma® (NCT01277523; 12 weeks; n=392 adolescents; severe asthma). ICS doses ranged from 200- to 1600-µg budesonide or equivalent. All trials permitted leukotriene receptor antagonists (except GraziaTinA-asthma®). Primary or secondary endpoints included change from baseline (response) in peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1.

Results: Overall, 925 patients received TioR 2.5µg, and 951 received pboR. TioR 2.5µg+ICS significantly improved peak $FEV_{1(0\text{-}3h)}$ response over placebo (GraziaTinA-asthma®: 159mL, P<0.0001; 2 replicate Mezzo TinA-asthma® pooled: 223mL, P<0.0001; RubaTinA-asthma®: 134mL, P=0.0085). Similarly, TioR 2.5µg+ICS+controller medications improved peak $FEV_{1(0\text{-}3h)}$ response (PensieTinA-asthma®: 111mL, P=0.0457). Differences with placebo in trough FEV_1 response were 110mL (P=0.0028), 180mL (P<0.0001), 84mL (P=0.1307), and 115mL (P=0.0509), respectively. Adverse events were similar between groups.

Conclusions: TioR 2.5µg+ ICS or ICS+ controller medications improved lung function in adults and adolescents with asthma.

Funding: Boehringer Ingelheim

Evaluating blood eosinophils and exacerbation history to predict inhaled corticosteroid response in chronic obstructive pulmonary disease (COPD)

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Introduction: Inhaled corticosteroids (ICS) are used to reduce the rate of COPD exacerbations. Debate continues over using blood eosinophils to predict ICS response, with some suggesting a cut-off of ≥2% (Pascoe S et al. Lancet Respir Med 2015;3:435-42). In the WISDOM study (NCT00975195), this response was driven by patients with higher eosinophil levels (≥4% or ≥300 cells/µL) (Watz H et al. Lancet Respir Med 2016;4:390-8]). We analyzed WISDOM data stratified by prior exacerbations and eosinophil levels to determine if the ICS responder group could be better specified.

Methods: *Post hoc* analysis of the rate of moderate/severe exacerbations after complete ICS withdrawal using a negative binomial regression model to estimate exacerbation rate according to number of prior exacerbations (<2 [n=1454] and ≥2 [n=841], estimated based on the number of courses of antibiotics or steroids in the past year) and eosinophil subgroups. The difference in exacerbation rate between the ICS-withdrawal and ICS-continuation groups (rate ratio [RR]) was compared within the subgroups defined by eosinophil count and exacerbation history.

Results: High eosinophil counts (≥400 cells/µL) were associated with increased exacerbation rate after complete ICS withdrawal only in patients with ≥2 prior exacerbations (n=86; RR=2.96), but not in patients with <2 prior exacerbations (n=161; RR=1.25).

Conclusions: Withdrawal of ICS only increased the rate of exacerbations in patients with both raised eosinophils (≥400 cells/µL) and a history of frequent exacerbations. In patients who do not meet these criteria, ICS may not be as effective as is commonly assumed.

Funding: Boehringer Ingelheim

Tiotropium add-on therapy has a safety profile comparable with that of placebo in children and adolescents with symptomatic asthma

Christian Vogelberg, Michael Engel, Petra Moroni-Zentgraf, Olaf Eickmeier

Introduction: The safety and tolerability of once-daily tiotropium add-on therapy was assessed in a pooled analysis using data from patients aged 1-17 years with symptomatic asthma of different severities.

Methods: The Phase II/III trials included were: NCT01634113, NCT01634139, NCT01634152, NCT01277523, and NCT01257230. The study duration ranged 12-48 weeks. Patients had persistent asthmatic symptoms (NCT01634113) or persistent asthma of moderate (NCT01634139, NCT01257230) or severe (NCT01634152, NCT01277523) intensity. Once-daily tiotropium 5µg or 2.5µg (2 puffs of 2.5µg or 1.25µg) or placebo (2 puffs) was administered as add-on to inhaled corticosteroids, with/without other background therapies. Treatment-emergent adverse events (AEs) occurring between the intake of first trial medication to until 30 days after the last dose were recorded.

Results: Overall 1696 patients were randomized and 1691 were treated: 1-5 years, n=101; 6-11 years, n=801; 12-17 years, n=789. Baseline demographics and disease characteristics were comparable between treatment groups. Overall, 52% patients (n=879) experienced any AE. Incidence of AEs was similar across tiotropium (50.5%) and placebo (53%) arms in patients aged 6-17 years and lower in the tiotropium groups (56.7%) than placebo (73.5%) in those aged 1-5 years. Most common AEs (n≥5%) were asthma worsening/exacerbation, nasopharyngitis, decreased peak expiratory flow rate, and viral respiratory tract infection. A majority of AEs were mild/moderate in intensity. Frequency of drug-related AEs, AEs leading to discontinuation, and serious AEs were low and comparable across the treatment arms. No deaths were reported.

Conclusions: Safety profile of tiotropium add-on therapy is comparable to placebo in patients with symptomatic asthma aged 1-17 years.

Funding: Boehringer Ingelheim

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: According to the CDC, in 2014 there were 17.7 million (7.4%) adults and 6.3 million (8.6%) children living with asthma in the US. Asthma guidelines recommend periodic assessment and management of symptoms to prevent exacerbations, the most severe of which can lead to hospitalization, increased healthcare utilization and cost. Some asthmatics have difficulty with achieving disease control, and despite treatment with effective controller agents including inhaled corticosteroids, and sometimes biologics for severe asthma patients, these patients experience an average of 2 exacerbations annually. In addition, according to recent data from Petsky et al. (Cochrane Reviews 2016), when FeNO is incorporated into asthma management, the risk of asthma exacerbations is reduced by 40-50%.

Methods: Using a decision analysis, the short-term cost-effectiveness of two alternatives to asthma management was compared: FeNO measurement in addition to standard of care management and the current standard of care without FeNO measurement. 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 associated with the two asthma management strategies.

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 the dominant asthma management strategy.

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

Funding: 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 underlying asthma severity, airway inflammation and risk for future asthma exacerbations. We hypothesized that adding the measurement of fractional exhaled nitric oxide testing (FeNO) to the patient's clinical assessment at the point of care and will provide insights into underlying airway inflammation. This added information helps practitioners to improve asthma control by making stepwise changes in anti-inflammatory treatment.

Method: Physicians were invited to participate if they had not used FeNO before in their practice. Physician assessed the likelihood of airway inflammation using clinical measures. Patient's FeNO was then determined using a NIOX® device. 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 available for analysis. Clinical impression of airway inflammation matched the actual FeNO in 4,457 patients (56.4%). Anti-inflammatory treatment was changed based on the FeNO result in 2,429/7,901 patients (30.7%). High FeNO group of 852 patients (83.90%) were on ICS, ICS/LABA or OCS therapy versus the Low FeNO group of 3312 patients (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.

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