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All Scientific Posters will be on display in the South Ballroom Foyer and Ponce de Leon 5 & 6, Friday, September 7th and Saturday, September 8th, 2018. Authors of these posters are requested to be at their poster to discuss their work from 9:30 – 11:00 AM, both Friday and Saturday.

Not for CME Credit

Are chest radiographs routinely indicated after chest tube removal following non-surgical placement?

Raiko Diaz, Krunal Bharat Patel, Saketh P. Shekar, Patricia Almeida, Jinesh P. Mehta

The insertion and subsequent removal of chest tubes are frequently performed procedures for management of multiple medical conditions. Chest radiographs after removal of a chest tube are commonly done to rule out interval development of a pneumothorax. This practice has been questioned in various retrospective and prospective studies done in surgical patient populations.

A 4-year retrospective study was conducted using the Cleveland Clinic and affiliated hospitals data. A chart review was performed and 1032 number of patients were screened, of which 200 patients were included. Inclusion criteria included adults who underwent chest tube insertion for medical reasons. Exclusion criteria were: any patient who underwent chest tube placement for a surgical reason, or who underwent surgical intervention prior to the chest tube being removed, any patient who did not have a CXR after chest tube removal.

Of the 200 patients that were included in the study, only 3 patients required chest tube re-insertion. Out of the 3 patients, all 3 were symptomatic (2) or had significant hemodynamic changes after the chest tube was removed (1). In all 3 cases symptoms manifested prior to the CXR being done; therefore, decision to reinsert the chest tube was made based on clinical signs rather than imaging. Out of the 200 patients included in the study, 53 had a CXR after chest tube removal showing a residual pneumothorax. Fifty out of the 53 patients ended up not needing chest tube re-insertion as patients had no symptoms and were hemodynamically stable. As expected, the practice of repeating a CXR after removal of chest tube resulted in delayed discharge.

Our study findings correlate with prior studies. Symptoms and hemodynamic data seem to be a better predictor of whether the patient will require chest tube re-insertion.

1

The prevalence of unexpandable lung in malignant pleural effusions

Todd Gandy and J. Terrill Huggins

Introduction: A recent multi-center prospective trial demonstrated a pleurodesis success rate of 43% after administration of talc in patients with malignant pleural effusion (MPE) who achieved a minimum of 75% pleural apposition following pleural fluid drainage. In the the present study, we reviewed a series of consecutive MPE where pleural manometry was performed to determine the prevalence of unexpandable lung.

Methods and Measurements: We identified 70 consecutive patients with MPE at the Medical University of South Carolina who underwent therapeutic pleural drainage with concomitant use of pleural manometry. We reviewed the Pressure/Volume curves (P/V) as well as the pre- and post-procedural chest radiographs (CXR) of these patients. Pleural manometry was performed consistent with the technique previously described by Doelken et al (Chest 2004).

Results: Abnormal pleural space elastance (P_{el}) was identified in 36 of 70 (51.4%; 95% CI, 39.2%-63.6%) patients. Twenty-seven of 36 (75%) patients with abnormal P_{el} demonstrated a biphasic P/V curve (partially expandable lung), while 9 of 36 (25%) demonstrated a monophasic P/V curve with increased P_{el}. Volume loss or post-procedural pneumothorax was uncommon in the abnormal P_{el}. and post-procedural pneumothorax was seen in 22% of cases.

Conclusions: Abnormalities of lung re-expansion based on pleural manometry are common in MPE and was seen in up to 50% of cases. This finding may have clinical implications when implementing rapid treatment strategies by identifying patients who are poor candidates for early pleurodesis. The variability in pleural manometric findings in patients with MPE may provide a physiologic explanation for the variability in pleurodesis success rates in MPE.

2

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasiab (DIPNECH): Our institutional experience with somatostatin analog therapy

Nagendra Y. Madisi and Maria. L. Padilla

Introduction: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare pulmonary condition with clinical manifestations of cough and slowly progressive dyspnea associated with obstructive physiology. It is characterized histologically by diffuse pre-invasive pulmonary neuroendocrine cell hyperplasia, often in conjunction with carcinoid tumors and tumorlets. Radiologically, patchy ground-glass opacities (GGO), mosaic attenuation, and pulmonary nodules are typical findings. Patients usually have stable to slowly progressive disease, but ~26% experience clinical and/or radiographic deterioration. Limited data is available on the disease evolution and treatment modalities. Association with pulmonary neoplastic disease has been described (Adenocarcinoma, SCC, malignant carcinoid). Here we report our experience with long term out come and disease progression in a cohort of DIPNECH patients with somatostatin analog (SSA) therapy.

Methods: In a cohort of 14 patients with DIPNECH seen at our institution from 2007 to-date, treated with SSA, we assessed clinical, radiographic, physiological parameters and outcomes of therapy.

Results: A total of 14 patients were diagnosed with DIPNECH. Majority of the subjects were female 13/14(92%) with a mean age of 69.9years and most were non-smokers 10/14(71%). Presenting complaint was cough in 42% and dyspnea in 58% of patients. Pulmonary nodules were seen on imaging in 13/14, and GGO in 4/14patients. Diagnosis was made by a surgical biopsy in 92% and endobronchial biopsy in 8% of patients. All patients received SSA therapy. The disease remained stable in 13/14 patients, but one patient had worsening lung function and cough while on SSA. Diarrhea and abdominal discomfort were reported in minority of patients on SSA therapy. Metastatic malignancy was diagnosed in 3/14 patients after receiving SSA (breast, brain and bladder), and there were no deaths in the cohort.

Conclusion: DIPNECH is a female predominant lung disease and is regarded as a precursor lesion of neuroendocrine lung tumors. Clinical course is variable; ranging from slowly progressive functional decline to long-term stability. Available data on management of these patients and long-term outcomes of SSA therapy from small case series and reports is conflicting.
Our experience with SSA therapy in DIPNECH was reassuring with improvement in presenting symptoms and stability in pulmonary function. Given the rarity of this disease, there is no consensus led guidelines for the treatment and management of DIPNECH. We recommend considering SSA in the treatment of DIPECH as this is a pre-neoplastic condition, however the safety and efficacy of SSA is unknown. Further research is warranted to help guide with the treatment to improve overall outcome.

3

Association of cardiopulmonary disease in patients with 'out of proportion' hypoxemia on home sleep testing

Saketh Palasamudram Shekar, Ramey Alfarra, Apurva Gandhi , Anas Hadeh

Introduction/ Rationale: Obstructive sleep apnea (OSA) is a disorder where a person stops breathing during sleep resulting in significant cardiovascular comorbidities. It is occasionally noted that the degree of desaturation is not proportional to the severity of OSA on Home sleep testing (HST) and thus the rationale of the study, to determine the relationship of cardiopulmonary disease in patients with 'out of proportion hypoxemia' to the severity of OSA.

Methods: A retrospective chart review abstracting data from patients undergoing HST at Cleveland clinic sleep disorder center was performed. HST conducted for 2 years were evaluated and patients undergoing HST who had either a pulmonary function test (PFT) or an echocardiogram within 3 months before or after were included. Data on apnea-hypopnea index (AHI), time of desaturation under 89%, forced expiratory volume in one second(FEV1) less than 50%, diffusion capacity of lung for carbon monoxide(DLCO) less than 60%, total lung capacity(TLC) less than 65%, right ventricular systolic pressure(RVSP) more than 30 mmHg and left ventricular ejection fraction(LVEF) less than 45%, body mass index(BMI) more than 45 were collected and were labelled as indicative of moderate to severe cardiopulmonary(CP) disease and the rest as having no or mild cardiopulmonary disease(No CP). Patients were further classified into mild (AHI 5-15), moderate (15-30) or severe (more than 30) OSA.

Results: Of the 239 patients identified to have undergone HST, 200 patients were diagnosed to have OSA of various degrees. AHI between CP and No CP groups did not differ significantly- 17.25 v/s 22.2 (P=0.293). Significant hypoxemia was discovered in CP group compared to No CP group with 11.6% median time spent under 89% oxygen saturation in the former v/s 5.5% in the latter group (P=0.0008).
Time spent under 89% oxygen saturation between the two studies groups were compared in each OSA severity using Mann- Whitney U test. There was a significant difference in mild OSA group- 8.65 % v/s 1.15 % total recording time with p <0.00018. No statistical significance was found between the groups in moderate and severe OSA. The threshold of significant desaturation in CP group was obtained by performing median splitting with 8.65% desaturation as the cutoff.

Conclusions/Clinical implication: Patients who had mild obstructive sleep apnea with hypoxemia of more than 8.65% of total recording time on home sleep testing should undergo cardiopulmonary evaluation and possibly in-lab CPAP titration.

4

Investigating the influence of caffeine intake and the incidence of ICU delirium

Christopher D'Angelo, Saketh Palasamudram Shekar, James B Gleason,. Lori Milicevic, Samantha Gillenwater, Jinesh Mehta

Learning Objectives/Background: ICU delirium is associated with prolonged intubation, increased length of stay, and higher mortality. Among the many factors which can influence ICU delirium we investigate caffeine. Most ICU patients can be considered in a state of relative caffeine withdrawal due to abrupt cessation of caffeine intake at the onset of ICU admission. In our small retrospective, proof of concept, study we investigated the association of caffeine on ICU Delirium.

ethods: A small retrospectively evaluated cohort of 100 patients admitted to Cleveland Clinic Florida Medical ICU from July to December 2017 were assessed by recording CAM-ICU status (a validated and commonly used score for monitoring the ICU delirium) and the amount of caffeine they consumed daily, prior to admission. Collected variables also included age, sex, primary ICU diagnosis, past medical history, ventilator days, ICU length of stay, as well as use of sedatives or pain medications. Statistical tests used in our analysis included one-way ANOVA. Caffeine consumption was calculated via the assistance of our inpatient pharmacy staff using caffeineinformer.com.

Results: A total of 98 patients were enrolled in the study (2 patients had no results recorded). Overall mean caffeine intake for the 38 CAM-ICU positive patients was 295 mg per day, and 192 mg per day in the 60 CAM- ICU negative patients. 63 % of the CAM-ICU positive patients were male and 37 % were female. Average age in the CAM-ICU positive group was 62. In the CAM-ICU negative group, 65% were male and 35% were female. Average age was in the CAM-ICU negative group was also 62. In regards to sedative use and mechanical ventilation, the majority of CAM ICU positive patients were both sedated and mechanically ventilated. ANOVA identified CAM-ICU positive patients to have a significantly higher daily caffeine intake, with a p value of 0.015.

Conclusions: ICU delirium is a common and well recognized complication of critical illness. Its development can delay successful extubation and hospital discharge. Moreover, it is associated with higher in-hospital and out-of-hospital mortality rates. While numerous factors likely contribute to the development of ICU delirium our data identifies a positive association between caffeine intake and ICU Delirium using CAM-ICU score. Being a commonly used substance, caffeine's withdrawal symptoms are well documented and its abrupt cessation may contribute to the development of delirium. While it is unknown whether supplementing caffeine in those with higher chronic daily intake will have an impact on the incidence of ICU delirium, our results do identify the need for ongoing study of this relationship. We speculate that there may be benefit in the prospective investigation of caffeine supplementation in ICU populations with elevated chronic caffeine intake.

5

Reducing rates of readmission and development of an outpatient management plan in pulmonary hypertension: Lessons from congestive heart failure management

Justin Dolan, Jinesh Mehta, Viviana Navas, James Tarver, Murali Chakinala, Franck Rahaghi

AIM: Pulmonary Hypertension (PH) currently has minimal guidelines for outpatient disease management. Congestive heart failure (CHF) however has studies which have shown effectiveness of disease management plans in reducing all-cause mortality and all-cause and CHF related hospital readmissions. Heart failure exacerbation is a common reason for readmission in both PH and CHF. The aim of this abstract was to review individual studies and comprehensive meta-analyses to identify effective CHF interventions that can be used to develop a similar disease management plan for PH.

METHODS: A comprehensive review of literature performed from 1993 to 2012, including original trials and meta-analysis and reviews. We reviewed the topics of outpatient CHF interventions to decrease CHF mortality and readmission and patient management strategies in CHF.

RESULTS: The most studied interventions included case management (CM-specialist nurse driven, education pre/post discharge, specialist nurse home visits, scheduled telephone calls for symptom management, when to seek help), multidisciplinary Intervention (MI-coordinated interventions and communications; specialist nurse driven, patient-caregiver education regarding disease, medication and diet, nurse clinic visits, regular telephone calls, individualized follow-up plan, access to physician, nurse, dietician, pharmacist, social worker), remote monitoring programs consisting of structured telephone strategy (STS-monitoring collected data via human-human or human-machine interactive response system) or tele-monitoring (TM-physiologic data transmission of electrocardiogram (EKG), blood pressure, weight, respiratory rate digitally). Clinic visits did not have a significant effect on CHF readmission or mortality. CM showed decreased all-cause mortality (ACM) at 12 months, all-cause readmission (ACR) at 12 months and CHF readmission at 6 and 12 months. MI resulted in decreased ACR and CHF readmission. There was some discrepancy on effectiveness of TM programs alone in individual studies, however large meta-analysis suggests TM provided a reduction in ACM and risk of CHF hospitalization. STS had similar results to TM including decreased risk of CHF hospitalization, without an effect on mortality.

CONCLUSIONS: Extrapolating from CHF data, it seems that strategies to improve the health of PH patients and the development of comprehensive care programs (CCP) should include structured telephone strategy and/ or tele-monitoring, case management strategies and multi-disciplinary interventions.

6

Lymphangioleiomyomatosis (LAM) of the uterus: Risk of pulmonary LAM?

K. B. Ascher and M. K. Glassberg Csete

Introduction: Lymphangioleiomyomatosis (LAM) is a rare disease affecting the lungs in most cases. It typically presents in young women with dyspnea, chest pain, hemoptysis, pneumothoraces, and severe respiratory failure. Virtually all cases of extrapulmonary LAM have asymptomatic or symptomatic pulmonary LAM diagnosed by pathognomonic cystic changes on high-resolution computerized tomography scan (HRCT). We report an unusual case of a woman with primary pelvic LAM without evidence of pulmonary involvement.

Case Report: A 27-year-old female with sporadic tuberous sclerosis complex (TSC) diagnosed by genetic testing underwent yearly screening renal ultrasound for angiomyolipomas. Ultrasound did not reveal renal disease, but rather a large solid moderately vascular pelvic mass related to the superior uterus. A magnetic resonance imaging (MRI) of the pelvis showed a solitary dominant intramural fibroid of the fundus with dimensions: 9 x 9 x 8 cm in transverse, anteroposterior, and craniocaudal respectively (Image 1). There was predominantly low-T2 signal with scattered small cystic spaces. Only the solid components of the mass enhanced with contrast; the cystic areas did not. The mass was surgically resected without complications. Due to the patient's history of TSC, immunohistochemical stains for Factor VIII and human melanoma black-45 (HMB45) with appropriate control were performed. Factor VIII immunohistochemical stains highlighted simple endothelial lining in the mural vascular channel proliferation. The vascular lesions within myometrium showed positive reactivity for HMB45. This staining pattern confirmed presence of myometrial LAM. Once confirmed by second pathology review the patient was started on sirolimus and referred to the LAM clinic for assessment of pulmonary-related LAM. The patient did not have any respiratory symptoms and HRCT chest failed to demonstrate pulmonary LAM. Pulmonary function tests (PFTs) were within normal limits. Sirolimus was discontinued due to absence of respiratory symptoms, radiological evidence of pulmonary LAM, or PFT abnormalities.

Discussion: LAM is predominantly a disease involving lung parenchyma that may have extrapulmonary involvement. Cases reported of myometrial LAM had symptomatic or asymptomatic pulmonary LAM. Case series of treatment with everolimus 10mg/day demonstrated regression of pelvic LAM. There is one reported case of extrapulmonary LAM without pulmonary involvement related to hepatic LAM treated with surgical resection without sequelae after one-year follow-up. We report a rare case of primary myometrial LAM in a female patient with TSC without evidence of pulmonary involvement. In these cases, without pulmonary involvement, surgical resection may be considered curative. The role of sirolimus in these cases is unknown.

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Anti-melanoma differentiation-associated gene 5 (MDA-5) linked Interstitial Lung Disease: A poor prognostic factor

Stefanie Purdon and Marilyn Glassberg

Introduction: The association between interstitial lung disease (ILD) and rheumatologic disorders is well-established, yet often difficult to diagnose correctly leading to a delay of diagnosis and treatment. The approach to treatment, however, relies on case reports and remain unproven due to a lack of randomized, double-blind trials. This is especially true for rare diseases and is true for this case we present of a woman with positive anti-melanoma differentiation-associated gene 5 (anti-MDA-5), interstitial lung disease (ILD) and myositis.

Clinical Case: A 73-year-old Israeli woman with a history of significant tobacco abuse with complaints of cough and exertional dyspnea for over one year developed acute worsening of her symptoms six months prior to consultation. At that time, her shortness of breath was presumed to be post-viral infection. After six weeks of symptoms, her primary physician ordered a chest computed tomography scan (Chest CT), pulmonary function testing (PFTs) and six-minute walk test (6MWT) as well as an esophagogastroduodenoscopy (EGD). EGD revealed esophagitis and gastritis for which omeprazole was initiated. PFTs showed FVC 57%, FEV1 63%, TLC 73% and diffusion capacity (DLCO) 36%. Patient walked 323 meters without evidence of oxygen desaturation. Chest CT showed ground glass opacities (GGO) and pattern consistent with NSIP, mediastinal and bilateral hilar lymphadenopathy, scattered pulmonary nodules and areas of complete bronchial opacification. Patient was then referred to the ILD Clinic. Previously reported pertinent physical exam findings included small telangiectasias and petechiae. ILD Clinic pertinent findings included decreased tear pools bilaterally, oropharynx with dry mucous membranes, lungs with right greater than left diffuse rales in upper and lower lung zones with inspiratory squeaking in the right lower lobe. Extremities with significant clubbing of upper extremity digits bilaterally. Serology demonstrated an anti-nuclear antibody (ANA) 1:80 in a speckled pattern; positive SSA Ab IgE of 50 units (Normal is less than 20 units) and MDA-5 antibody of 50 units (Normal is less than 20 units) and Quantitative IgG 2307 mg/dL. Repeat PFTs at time of consultation showed decline in lung function with FVC of 50% predicted, FEV1 59% predicted, TLC of 60% predicted, and DLCO of 29% predicted. She required 2LPM supplemental oxygen with exertion to maintain an oxygen saturation about 89%. Echocardiogram was significant for mild diastolic dysfunction. CT Chest showed increased bilateral GGO. She was started on oral prednisone 20mg PO daily. Risks and benefits of experimental immunomodulatory therapy were discussed. The patient began mycofenolate mofetil (Cellcept) 500mg PO twice daily with CBC and comprehensive metabolic profile every six weeks. Cellcept dose was increased as tolerated to 1g twice daily after one month with steroid dose tapering at that time. She has had no further hospitalizations or exacerbations to date.

Clinical Lessons: Increasing awareness of anti-MDA-5 gene and its association with ILD and myositis is important to reduce a delay in diagnosis and for treatment initiation for future proven therapies.

Discussion: Myositis, an inflammatory process involving muscle and skin, includes polymyositis and dermatomyositis. This system of classification limits clinicians when attempting to diagnose and treat the subset of patients with atypical signs/symptoms or laboratory values, but with clinically suspicious features such as the patient in this case. Many of the patients that carry a diagnosis of inflammatory myopathy will develop ILD.

Small studies have shown that the presence of MDA5 antibodies, worsening radiographic evidence of ILD, and ethnicity are some of the risk factors that correlate with poor prognosis[2]. Treatment of myositis-associated ILD includes two phases: Induction phase (includes steroid +/- induction therapy and is dependent upon the severity of disease) and maintenance phase (first line therapy includes oral glucocorticoids and cellcept or azathioprine). These treatments improve lung function (FVC and DLCO)[3] in case reports. In addition, exercise/rehabilitation programs are safe and may increase quality of life and decrease inflammat

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Extraskeletal pulmonary osteosarcoma masquerading as tuberculosis

Yoslay Perez, Rene Rico, David Ashkin and Andreas Schmid

Introduction: Extraskeletal osteosarcoma is a rare mesenchymal malignant tumor that most often presents as an enlarging soft tissue mass in the lower extremities. We present a case of an extraskeletal osteosarcoma of the lung referred to our institution for the management of pulmonary tuberculosis.

Case Report: A 61-year-old Caucasian man presented to an outside hospital for evaluation of weakness, weight loss and cough. He had a 40-pack year history of cigarette smoking and extensive travel history without exposures to tuberculosis or congregate living. The patient underwent liver transplantation 12 years prior for alcoholic liver cirrhosis and was on immunosuppressive therapy. On examination he was afebrile, well appearing with normal vital signs, pulmonary, cardiac and abdominal examinations. Labs were significant for elevated transaminases due to acute T-cell mediated rejection diagnosed by liver biopsy. A computed tomography (CT) of the chest showed extensive bilateral centrilobular tree-in-bud nodularity and a cavitary lesion in the right upper lobe suggestive of tuberculosis. A bronchoscopy with bronchoalveolar lavage was negative for Acid-Fast Bacilli (AFB) smear but with a reverse transcription polymerase-chain-reaction (RT-PCR) that was weakly positive but subsequently culture negative. Initial trans-bronchial biopsies showed necrotic material. The patient was transferred to our institution to start liver sparing tuberculosis treatment. Repeat CT chest after eight weeks of therapy showed an enlarging lung mass (Figure 1). The patient underwent CT guided biopsy of the mass with pathology consistent with high-grade osteosarcoma. Positron emission tomography (PET) CT showed a hypermetabolic lesion in the right upper lobe without distant lesions. The patient was referred to oncology for the management of high-grade extraskeletal osteosarcoma of the lung.

Discussion: Extraskeletal osteosarcoma accounts for 1% of all soft-tissue sarcomas and 4% of osteogenic osteosarcomas [1]. They commonly present with an enlarging soft tissue mass [2, 3] with a mean age range of 47.5-61.0 years and a slight male predominance [4-9]. Most tumors occur in the lower extremities (48%), the upper extremities (8-23%), the retroperitoneal (8-17%), and the trunk (10-11%) [4-8, 9]. To our knowledge, only a handful of cases have been reported of intrathoracic extraskeletal osteosarcomas. This case had an interesting presentation with the weakly positive RT-PCR, which was at the threshold for detection (cut off is 36cycles, our patient was 35). It is important to recognize that a high cut off positive RT-PCR result has to be interpreted cautiously, not to miss other potential diagnoses such as this rare malignancy.

Melanoma and Sarcoidosis

Rene Rico, Yoslay Perez, Oriana Salamo, Mehdi MirsaeidI

Introduction: Sarcoidosis is a chronic systemic disease of unknown etiology leading to the formation of noncaseating granulomas in various organs, more commonly affecting the pulmonary, dermatologic, lymphatic ophthalmologic systems. Sarcoidosis is often referred to as the great mimicker, given their various forms of presentations and their simulation with malignancies as well as infectious processes. We present a case of sarcoidosis in a patient diagnosed with melanoma who experienced spontaneous resolution.

Case Report: A 61 year old man presented to the clinic complaining of dyspnea on exertion associated with a skin rash in the upper and lower extremities bilaterally. He denied any weight loss, sputum production or hemoptysis. He had a 25-pack year history of cigarette smoking. He underwent surgical excision of melanoma in the thoracic region of his back 7 years prior. On examination he was afebrile, well appearing with normal vital signs, pulmonary, cardiac and abdominal examination. His skin exam was notable for bilateral raised nodules in the upper and lower extremities. Laboratory data including Histoplasma antigen in urine, Cocciodiomycosis, Aspergillus and rheumatologic work up were unrevealing. A computed tomography (CT) of the chest showed bilateral pulmonary nodules with hilar lymphadenopathy. A biopsy of a skin nodule showed granulomatous dermatitis. A positron emission tomography (PET) CT showed diffuse hypermetabolic pulmonary nodules and skin lesions. Endobronchial ultrasound bronchoscopy with transbronchial biopsy and bronchoalveolar lavage (EBUS TBNA and BAL) was non diagnostic. Diagnosis of sarcoidosis was performed based on skin biopsy findings with granulomatous dermatitis and pulmonary sarcoidosis bases on computed tomography (CT). Patient was referred to dermatology after newly found skin lesion diagnosed to be melanoma by excisional biopsy. A repeat computed tomography (CT) of the chest at three and eleven month interval showed complete resolution of the previously identified pulmonary nodules.

Discussion: Sarcoidosis has been reported to be associated with both hematological as well as solid tumors. It has been reported in melanoma patients after treatment with immunotherapeutic agents, as well as those who did not receive systemic antineoplastic therapy. The diagnosis of sarcoidosis is often made simultaneously to the melanoma diagnosis or within a year difference; rarely does it precede the latter. There are several hypothesis thought to play a role in the pathogenesis of cancer and sarcoidosis. Among those, ultraviolet light is thought activate an inflammatory cascade contributing to both entities, however a definitive mechanism of pathogenesis is unknown.

Perivascular epithelioid cell tumors in lymphangiomyomatosis: A new association

Kantha Medepalli and Marilyn Glassberg

Introduction: Renal angiomyolipomas (AMLs) and perivascular epitheloid cell tumors, PEComas, are mesenchymal tumors made of perivascular epithelioid cells and members of the microphthalmia-associated transcription factor (MiTF) family of tumors. AMLs are the most commonly reported PE Comas associated with lymphangioleiomyomatosis (LAM). We present a case of a woman with LAM found to have an incidental finding of a left adrenal lesion during a workup for abdominal pain and sweating.

Case Report: A 49 years old woman of Hispanic origin, with known past medical history of LAM and hysterectomy with oophorectomy secondary to large uterine cysts and multiple ovarian cysts presented in pulmonary clinic with mild shortness of breath and new onset abdominal pain and hypertension. She was initially diagnosed with LAM in a chest computed tomography scan (CT) seven years prior when she presented with a spontaneous pneumothorax. Because of new abdominal pain and sweating, she underwent an immediate abdominal CT scan that demonstrated a left-sided adrenal lesion 4.3 x 2.8 x 1.9 cm in size with hypervascular appearance and multiple enhancing arterial vessels. Moderate blood was noted on her urinalysis. The patient was seen by the Endocrinology service. When the urinary catecholamine tests were negative diminishing the chance of a pheochromocytoma and the differential included possible malignancy, the patient chose to undergo a laparoscopic adrenalectomy rather than ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy. Histopathology was diagnostic of an adrenal PEComa negative for pancytokeratin, S100, GATA3, PAX8, CDX2, TTF1 inhibin, synaptophsin, chromogranin, myosin and TFE3; the stromal component was negative for Congo red stain. Given the small tumor size and absence of other factors including pleomorphism, mitotic activity and necrosis, this neoplasm was considered to have a more indolent behavior. The patient deferred treatment with sirolimus and genetic counseling revealed no evidence of tuberous sclerosis.

Discussion: PEComas are mesenchymal tumors with perivascular epithelioid cell differentiation with female predominance. The tumors are made up of nests and sheets of epithelioid cells as well as spindled cells. Typically they are found in retroperitoneal, visceral and abdominopelvic sites including the uterus, ovaries and pancreas. The cells have positive immunoreactivity for HMB 45 and/or melan A as well as positive immunohistochemical staining for □ smooth muscle actin or desmin markers. The tumors are usually benign, however, tumors > 5cm with high mitotic activity, necrosis, and high nuclear grade can be malignant. Surgical resection is the typical treatment.

To our knowledge, this is the first case of an adrenal P Coma reported in a patient with LAM, the latter more commonly reported in association with renal AMLs. While treatment for LAM has included sirolimus, no such therapy as of yet been shown to be effective for PEComas. For tumors that are suspicious for AML/PEComa, but negative or focally positive for HMB45 and melan-A, PNL2, a recently described sensitive and specific biomarker, may be a useful adjunctive study after surgical resection. Future research should be completed to elucidate underlying related biomarkers and signaling pathway that connects LAM and PEComas.

Massive Hemoptysis Associated with Mycobacterium Terrae Infection

A. Cabrera, M. Egozcue, H. Y. Vazquez, G. Ferrer

Introduction : Pulmonary nontuberculous mycobacterial disease (PNTMD) is increasing worldwide in developed and underdeveloped countries. Life threatening hemoptysis in PNTMD is usually of vascular origin and requires urgent intervention [1]. We present a case that highlight the importance of prompt recognition of bronchial artery aneurysms, role of diagnostic modalities and common therapeutic approaches.

Case presentation : A 56-year-old Hispanic woman presented with 1-week history of intermittent low-grade fever, productive cough, and hemoptysis. She had remote history of pulmonary tuberculosis successfully treated. Computed tomography (CT) of the chest showed parenchymal scarring within the right upper lobe. She had a flexible fiberoptic bronchoscopy, intra-procedure massive right upper lobe bleeding developed with an estimated blood loss of 175 ml. The bleeding was controlled. We consulted with interventional radiology service for bronchial angiography. The angiogram confirmed the presence of several right upper lobe bronchial artery aneurysms treated with embolization. The hemoptysis was resolved and the patient remained stable after the procedure.

The bronchoalveolar lavage (BAL) specimens where positive for Pneumocystis jirovencii and Acid-Fast Bacilli (AFB). The acid - fast bacilli was identified as Mycobacterium terrae at six weeks of culture. No recurrent hemoptysis has been reported at present.

Conclusion: The overall incidence of massive hemoptysis in non-tuberculous mycobacterial infection is not well described. In our case, flexible fiberoptic bronchoscopy and bronchial angiography helped in identifying the source of the bleeding and location of the aneurysms. Arterial trans-catheter embolization is the first line of treatment for massive hemoptysis originating from the bronchial circulation.

"Common Mold" pneumonia in an immunocompetent host

Zeeshan Chauhan, Usha Deonarine, Gustavo Ferrer

Introduction: Aspergillus niger and Penicillium sp, also known as "common mold," are often found on decaying fruits, vegetables and bread. They are ubiquitous in the indoor air of residential homes. However, they are rarely reported to cause pulmonary infection in the immunocompetent host.

Case Summary: We present a case of 56 years old Asian-American female with past medical history of diabetes and inflammatory bowel disease on mesalamine and prednisone presented with a chronic cough associated with worsening exertional dyspnea, unintentional weight loss and night sweats. Chest CT scan revealed 13 x 11mm Right upper lobe attenuation and 7mm subpleural non-calcified nodule as well as 5mm calcified nodule in the right middle lobe with right middle lobe and lingular bronchiectasis. Bronchoscopic evaluation and bronchoalveolar lavage, especially of the right upper lobe, showed pathological signs of acute inflammation and bronchoalveolar cultures revealed Aspergillus niger and Penicillium Sp. Rest of cultures including Acid fast Bacilli were negative. The patient was later hospitalized with worsening cough and dyspnea warranting treatment of cultured fungi. Parental therapy with voriconazole was initiated and then switched to oral voriconazole. Patient's pulmonary symptoms markedly improved with four weeks of optimum voriconazole therapy.

Conclusion: Aspergillus niger and Penicillium Sp are unlikely pathogens implicated in invasive pulmonary infection in the immunocompetent host, but antifungal therapy should be considered in appropriate clinical scenario. It is also essential to monitor voriconazole levels as it can have variable bioavailability.

Strict vegan diet leading to malnutrition and active tuberculosis (TB)

Usha Deonarine, Zeeshan Chauhan, Armando Cabrera, Asma Jafri, Gustavo Ferrer

Introduction: Cell mediated immunity is the basis of the body's defense mechanisms against mycobacterium tuberculosis. Effective cell mediated immunity requires effective adequate phagocytosis and T-cell function. Vitamin B12 and Vitamin D deficiency has been linked to impaired oxygen burst reaction, which is needed for effective phagocytosis. Experimental data has shown protein energy malnutrition to impair T-cell mediated immune pathways. Strict vegan and vegetarian diets are known to be lacking in cobalamin, protein and vitamin D.

Case Summary: We present the case of an immunocompetent 40-year-old female who presented to pulmonary clinic with a chronic intractable cough. Social history revealed that she adhered to a strict vegan diet for many years. After initial work up was inconclusive, bronchoalveolar lavage revealed AFB positive smears leading to the diagnosis of acute mycobacterial tuberculosis infection. Albumin levels were noted to be 2.8 g/dl during her admission, and Vitamin D was noted to be 29ng/ml. Molecular testing revealed an INH resistant strain of mycobacterium TB.

Conclusion: Certain studies have found a correlation between vegetarian diets and increased incidence of active TB. Additionally, vegetarian and vegan diets have been shown to alter our microbiome, an intrinsic part of our innate immunity. The long-term effects of these changes on the respiratory tract are yet to be elucidated. Further research is needed into the effects of vegetarian and vegan diets on the immune system.

A mystery within a mystery: A case report of carrington's disease presenting as painless icterus

Arnaldo Reyes, Nillian Zamot, Gustavo Ferrer, Hector Vazquez-Saad

Introduction: Chronic eosinophilic pneumonia (CEP) is a rare interstitial lung disease characterized by a clinical picture that is progressive and often severe with symptoms including high fever, elevated blood and alveolar eosinophils, weight loss, and peripheral pulmonary infiltrates. There are typically no major extrapulmonary manifestations of CEP[1].

Case Presentation: We present the case of a 57-year-old male veteran with no previous medical history presenting with one year history of shortness of breath, wheezing, exertional dyspnea and painless jaundice. He denied abdominal pain, nausea, vomiting, or history of asthma. No reported history of viral hepatitis exposure, blood transfusions, intravenous drug use, or recent travel. Blood workup revealed AST 1180U/L, ALT 1377U/L, total bilirubin levels of 24.6mg/dL, and absolute eosinophilic count of 0.72 K/cmm. CT scan of chest showed mediastinal lymphadenopathy, bilateral centrilobular nodules, and pleural-based nodular opacities. Endobronchial node biopsies showed increased eosinophils without granulomas. Laboratory results showed absolute eosinophil count of 0.6K/cmm, IgE levels of 396.8 IU/mL. However, Aspergillus IgE, precipitin and Antineutrophil cytoplasmic antibody (ANCA) were negative. Patient underwent a course of Prednisone 10mg for five days. Blood workup returned to normal limits after four days. Given the dramatic response, the patient was started on inhaled and systemic steroid therapy. Follow-up CT scan showed resolution of previous findings.

Conclusion: Patients with CEP show dramatic improvement in response to corticosteroid therapy[3]. However, studies show that relapse is equally common after 3-6 months of treatment. This raises the question of how soon should steroid sparing agents be considered.

Desquamative interstitial pneumonia in a non-smoker with neurofibromatosis type 1 (Von Recklinghausen Syndrome) – A case report

Ferrer G, Garcia C, Tazelaar HD, Saleh A, Arrossi AV.

Introduction: Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder that occurs in 1 per 3,000 individuals, caused by a mutation of the NF1 gene. Pulmonary involvement can occur in the form of interstitial fibrosis, emphysema, pulmonary hypertension and thoracic neoplasm. We report the first case of desquamative interstitial pneumonia (DIP) in a non-smoker with NF1.

Case presentation: A 42-year-old male, non-smoker with history of NF1 presented with a one-year history of cough and gradually worsening dyspnea on exertion. Symptoms transiently improved with a short course of Prednisone. He worked in information technology and never had environmental exposures. Physical examination revealed diffuse crackles, café-au-lait spots, neurofibromas and axillary freckles. The computed tomography of the chest showed peripheral ground glass opacities. Bronchoalveolar lavage cytology was markedly hypercellular with macrophages. Lung wedge biopsies showed numerous histiocytes within the airspaces and thickened alveolar interstitium by chronic inflammatory cells consistent with DIP. Patient responded well to a 6-month course of Prednisone taper.

Discussion: Interstitial lung disease (ILD) has been reported in NF1 with an incidence of 5.5 to 23%. [2,3] Ground glass opacities, cystic lesions and emphysematous changes are commonly described radiologic findings, but the association to NF1 is controversial as smoking was a confounder. [3,4] Although data is limited, in cases of NF1 with ILD documented with biopsy, histopathologic patterns reported include non-specific interstitial pneumonia (NSIP), [2] chronic eosinophilic pneumonia .[5] To the best of our knowledge, this is the first report of DIP-pattern of ILD in a non-smoker with NF1.

A Fortunate Accident: The unveiling of Factor G20210A mutation in an otherwise healthy female

Nillian Zamot, Arnaldo Reyes, Gustavo Ferrer, Hector Vazquez-Saad, Monica Egozcue

Introduction: Pulmonary Embolism (PE) remains the most common preventable cause of in-hospital all-cause mortality; responsible for approximately 10% of hospital deaths. Case fatality rates up to 30% after hospital discharge have been reported. Prothrombin G20210A mutation increases the risk for thrombosis, although the mechanism is not completely understood.

Case Presentation: We present a case of a 25-year-old female with history of pituitary adenoma status post resection, which presented to the emergency department (ED) with shortness of breath (SOB) for two days after being involved in a motor vehicle accident (MVA) five days prior. She sustained minor foot fractures requiring immobilization. She was incidentally found to have an IVC thrombus and was sent home on Enoxaparin, but the progressive SOB prompted the patient to visit the ED. Upon arrival the patient was tachycardic and hypoxic despite the use of a nasal cannula at 4L/min and the patient rapidly progressed into respiratory failure and cardiac arrest. Tissue plasminogen activator was administered and CT Angiography confirmed massive pulmonary emboli. Patient underwent emergent surgical embolectomy. Further investigation revealed Factor II (Prothrombin G20210A) mutation and the patient was discharge home on lifelong anticoagulation therapy.

Conclusion: PE remains a challenging diagnosis, more often missed than found. The prevalence of Prothrombin G20210A mutation differs in different countries and ethnic groups, being highest in Caucasians Heterozygous Prothrombin mutations are found in about 2% of the US white population. Identifying these mutations is essential to determine the management and outcomes of this patient population.

Successful use of mepolizumab in a patient with chronic eosinophilic pneumonia

Warit Jithpratuck , Panida Sriaroon, Vinny O Samuel

Summary and Lessons Learned: Chronic eosinophilic pneumonia (CEP) often poses a diagnostic challenge due to its overlapping presentations with other eosinophilic lung diseases. Patients with CEP typically present with gradual onset of cough and progressive shortness of breath over several months. Our patient presented with a 4-month history of cough and respiratory symptoms and had peripheral blood and bronchoalveolar lavage (BAL) eosinophilia. Chest radiographs revealed extensive infiltrations. Her CEP diagnosis was made after other causes of eosinophilic lung disease were excluded. She had a relapse when oral steroids were discontinued. Mepolizumab treatment led to excellent clinical response. We learned several lessons: Firstly, it is important to broaden differential diagnoses to include common and uncommon conditions. Secondly, CEP should be considered in the differential diagnosis of patients presenting with thick cast sputum production. Thirdly, we learned about challenges in the treatment of CEP. Lastly, mepolizumab can be considered an adjunct therapy in CEP patients who have frequent relapses or are steroid dependent

Patient Presentation and Testing: A 20-year-old female with history of asthma, environmental allergies, and eosinophilic esophagitis presented with productive cough and progressive shortness of breath for 4 months. Expectorated sputum often contained whitish yellowish casts. Inhaled corticosteroids and bronchodilator failed to improve symptoms or FEV1. White blood cell count (25,000/mm3), absolute eosinophil count (10,750/mm3 [43%]), and IgE level (1,122 IU/mL) were elevated. On chest CT, there were bilateral multifocal opacities, predominantly in the upper lobes. Pathologic examination of the casts retrieved during bronchoscopy revealed dense eosinophils and numerous Charcot-Leyden crystals. Blood, sputum, BAL, and stool specimens were negative for microorganisms. Extensive evaluation, including bone marrow examination, was used to determine the cause of eosinophilia. The diagnosis of CEP was made following negative evaluation for environmental or drug allergies, infections, parasitic infestations, hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis, and eosinophilic granulomatosis with polyangiitis.

Diagnosis, Treatment and Patient Outcomes: Initiation of empiric treatment with antibiotic, anthelminthic agent, and inhaled and systemic corticosteroids markedly improved respiratory symptoms. Relapse occurred when prednisone was stopped. Prednisone was restarted and continued for 6 months; her lowest AEC was 1,224/mm3. Ten months after the initial presentation, chest CT identified a new area of impaction in the bronchus with distal bronchiectasis. Mucinous plugs made of eosinophilic materials persisted in the bronchi. Within one month of starting mepolizumab injections, her spirometry parameters improved and she no longer experienced cough or expectorated thick casts. Over the next year of mepolizumab treatment, her respiratory symptoms remained stable, with no exacerbation or prednisone use.

AMPLIFY: A randomized, phase III study evaluating the efficacy and safety of aclidinium/formoterol versus monotherapy in patients with cOPD

Sanjay Sethi, Edward Kerwin, Henrik Watz, Gary T. Ferguson, Robert Mroz, Rosa Segarra, Eduard Molins, Diana Jarreta, Esther Garcia-Gil

Introduction: AMPLIFY aimed to further assess the efficacy and safety of aclidinium bromide/formoterol fumarate (AB/FF) vs monocomponents (AB and FF; NCT02796677). AMPLIFY also investigated the non-inferiority of AB vs tiotropium; these data will be presented elsewhere.

Methods: Phase III, 24-week, randomized, parallel, double-blind, active-controlled, multinational study. Symptomatic patients with moderate to very severe COPD were randomized to twice-daily AB/FF 400/12µg, AB 400µg, or FF 12µg or once-daily tiotropium 18µg. Assessments included: change from baseline in 1-h morning post-dose FEV_1 (co-primary endpoint: AB/FF vs AB); change from baseline in morning pre-dose FEV_1 (co-primary endpoint: AB/FF vs FF); $AUC_{0–3/3h}$ FEV_1; onset of action; exacerbations; health-related quality of life (HRQoL; St George's Respiratory Questionnaire and COPD Assessment Test); and safety.

Results: Analysis included 1,583 patients, mean age was 64.3 years and mean post-bronchodilator FEV_1 was 50.3% predicted. At Week 24, patients receiving AB/FF had significantly improved 1-h post-dose FEV_1 vs AB or FF, significantly improved trough FEV_1 vs FF, and significantly improved $AUC_{0–3/3h}$ FEV_1 vs AB or FF. Onset of action was significantly improved with AB/FF vs AB or FF as early as 5 mins. Exacerbations were reduced with AB/FF vs FF (not statistically significant). All treatments improved HRQoL. The incidence of treatment-emergent adverse events was similar between groups.

Conclusions: In symptomatic patients with moderate to very severe COPD, treatment with AB/FF significantly improved 1-h post-dose bronchodilation vs AB and trough FEV_1 vs FF.

Funding: Circassia

Effect of twice-daily Aclidinium/formoterol versus monotherapy or tiotropium on 24-hour bronchodilation and symptom control in patients with COPD: Results from AMPLIFY

Edward Kerwin, Sanjay Sethi, Gary T. Ferguson, Robert Mroz, Henrik Watz, Rosa Segarra, Eduard Molins, Diana Jarreta, Esther Garcia-Gil

Introduction: AMPLIFY (NCT02796677) assessed the efficacy and safety of aclidinium/formoterol (AB/FF) vs its monocomponents or tiotropium (TIO) in patients with COPD. Here we report symptom data from AMPLIFY and the results of a pre-planned sub-study evaluating 24-h bronchodilation in a subset of patients.

Methods: AMPLIFY was a Phase III, 24-week, randomized, parallel, double-blind, active-controlled, multinational study. Symptomatic patients with moderate to very severe COPD were randomized to twice-daily AB/FF 400/12µg, AB 400µg, or FF 12µg or once-daily tiotropium (TIO) 18µg. The effects of AB/FF vs AB, FF or TIO on 24-h bronchodilation were assessed in a subset of patients using serial spirometry (change from baseline in normalized area under the curve [AUC] FEV_1). Nighttime and early-morning symptoms were assessed in the primary analysis population using the Nighttime and Early Morning Symptoms of COPD Instruments.

Results: The primary analysis population included 1583 patients, of these 563 patients were included in the sub-study. $AUC_{0–24/24h}$ was significantly greater with AB/FF vs FF or TIO, and $AUC_{12–24/12h}$ was significantly greater with AB/FF vs all treatments. In the primary population, nighttime and early-morning symptoms showed numerical improvements with AB/FF vs all treatments. A number of statistically significant improvements were observed with AB/FF vs other treatments for individual symptoms at nighttime and early morning.

Conclusions: AB/FF provided significantly better bronchodilation 12–24h post-dose vs monocomponents or TIO. AB/FF demonstrated significant improvements in individual nighttime and early-morning symptoms vs other treatments in patients with moderate to very severe COPD.

Funding: Circassia

Effects of aclidinium bromide on major adverse cardiovascular events and copd exacerbations in patients with copd and cardiovascular risk factors

Robert Wise, Benjamin Scirica, David Schoenfeld, Sami Z. Daoud, Jonas Román, Colin Reisner, Esther Garcia Gil, Kenneth Chapman

Introduction: Evaluation of the long-term effects of aclidinium bromide 400µg twice-daily vs placebo on cardiovascular (CV) safety and exacerbations in patients with moderate to very severe COPD and a history of cerebrovascular, coronary, or peripheral artery disease, or the presence of ≥2 CV risk factors.

Methods: ASCENT COPD (NCT01966107), a Phase IV, double-blind, randomized, placebo-controlled, parallel-group study of 452 sites in USA/Canada. Primary safety and efficacy variables were time to first major adverse CV event (MACE: CV death, non-fatal MI, or non-fatal stroke), and rate of moderate to severe COPD exacerbations during the first year. The study was terminated after ≥122 MACE (3 year maximum study duration) in order to achieve 90% power to rule out a hazard ratio (HR) of 1.8 in time to first MACE for aclidinium vs placebo.

Results: Analysis included 3589 patients. There was no increased risk of MACE, or of MACE or other serious CV event of interest, with aclidinium vs placebo (HR, [95% confidence interval]: 0.89, [0.64-1.23], and 1.03, [0.83-1.28], respectively). There was a 22% reduction in moderate to severe exacerbation rate with aclidinium vs placebo ($p<0.001$), and a 35% reduction in hospitalizations due to COPD exacerbation ($p<0.01$) during the first year of treatment. AEs incidence was comparable between groups.

Conclusions: No increased risk of MACE in at-risk patients receiving aclidinium vs placebo with moderate to very severe COPD was found. In addition, the risk of moderate to severe exacerbations and associated hospitalizations was reduced significantly with aclidinium vs placebo.

Funding: Circassia

Effect of nintedanib on exercise capacity in patients with idiopathic pulmonary fibrosis (IPF): Results from a Phase IIIb trial

Lisa Lancaster, Craig S Conoscenti, Jonathan Ilowite, Matthias Trampisch, Mitchell Kaye

Introduction: We used data from a Phase IIIb trial to assess the effects of nintedanib on changes in exercise capacity and arterial oxygen saturation during exercise in patients with IPF.

Methods: Patients with a diagnosis of IPF within 5 years, FVC ≥50% predicted and DLco 30–79% predicted were randomized to receive nintedanib 150 mg bid or placebo double-blind. Changes from baseline in 6-minute walk test distance (6MWD) and in oxygen saturation nadir (lowest observed SpO_2 during the test) at month 6 were assessed. Analyses were exploratory and descriptive.

Results: In total, 113 patients were treated (56 with nintedanib, 57 with placebo). Baseline, mean (SD) 6MWD was 345 (141) m and 348 (146) m in the nintedanib and placebo groups, respectively. Mean (SD) oxygen saturation nadir was 89.6 (2.7)% and 89.7 (2.7)% in these groups, respectively. At month 6, adjusted mean (SE) absolute changes from baseline in 6MWD were +5 (11) m in the nintedanib group and –13 (11) m in the placebo group (based on data from 55 and 52 patients, respectively) (difference 18 m [95% CI: −14, 50]). Mean (SD) changes from baseline in oxygen saturation nadir at month 6 were 1.2 (5.4)% in the nintedanib group and 1.4 (3.1)% in the placebo group (based on data from 46 patients in each group).

Conclusions: These findings from a Phase IIIb trial suggest that in patients with IPF, treatment with nintedanib for 6 months was associated with an improvement in exercise capacity compared with placebo.

Funding: Boehringer Ingelheim

Survival in patients with idiopathic pulmonary fibrosis (IPF): Data from the IPF-PRO Registry

Laurie Snyder, Scott Palmer, Megan L Neely, Thomas Leonard, Craig S Conoscenti

Introduction: IPF is a progressive and ultimately fatal interstitial lung disease with a variable clinical course. We assessed relationships between clinical characteristics and death in patients with IPF.

Methods: Data from patients with a newly established diagnosis of IPF enrolled in the US Idiopathic Pulmonary Fibrosis Prospective Outcomes (IPF-PRO) Registry from its inception on 5 June 2014 to 26 October 2017 were used to examine relationships between patient characteristics at time of enrolment and death. Univariable associations were assessed using Cox proportional hazards models.

Results: Among 662 patients enrolled in the registry, 91 deaths were observed over a follow-up period of 30 months. Oxygen use at rest (HR 4.51 [95% CI: 2.94, 6.93]), oxygen use with activity (HR 3.41 [95% CI: 2.23, 5.21]), history of pulmonary hypertension (HR 2.30 [95% CI: 1.28, 4.15]) and prior all-cause hospitalization (HR1.69 [95% CI: 1.09, 2.61]) were significantly associated with death. The risk of death increased per 5-year increase in age in patients aged ≥62 years (HR 1.39 [95% CI: 1.29, 1.50]) and decreased per 5-year increase in age in patients aged <62 years (HR 0.46 [95% CI: 0.37, 0.56]).

Conclusion: Univariable analyses of data from the IPF-PRO Registry suggest that oxygen use, particularly oxygen use at rest, is a strong predictor of death in patients with IPF.

Funding: Boehringer Ingelheim

Decreased exacerbations and improvement in asthma symptom control in asthma COPD overlap (ACO) treated with omalizumab: Data from the prospero cohort study

Nicola A. Hanania, Bradley E. Chipps, Noelle M. Griffin, Benjamin L. Trzaskoma, Ahmar Iqbal, Thomas B. Casale

Introduction: Patients with asthma COPD overlap (ACO) are often excluded from asthma/COPD clinical trials. PROSPERO (Prospective Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab), an open-label, real-world study, did not exclude ACO patients, which provides an opportunity to understand real-world outcomes in ACO patients.

Methods: 56 ACO patients from 737 adults in the PROSPERO cohort (N=806) followed for up to 48 weeks. Omalizumab candidates were chosen via physician need assessment and accessed omalizumab via insurance/other funding. At baseline and on study, asthma-related healthcare utilization, including exacerbations (symptom worsening requiring oral corticosteroid burst, emergency department visit or hospitalization), was recorded. Asthma control was recorded monthly (Asthma Control Test [ACT]). Spirometry and biomarkers (FeNO, blood eosinophils) were recorded at baseline, 6 months, and study end.

Results: At baseline, ACO patients had mean (SD): age=57.6 (10.9), baseline post-bronchodilator % predicted FEV1=68.5% (19.2%), FEV1/FVC=66.7% (11.8%), reversibility=11.6% (12.5%). Median (range) blood eosinophils were 200 (40-760) cells/μL vs 220 (0-2340) cells/μL in the adult asthma cohort. In ACO patients 12 months after initiating omalizumab, mean (SD) exacerbations decreased (from 12.8 [4.7] 12 months before omalizumab to 1.1 [1.4]) and ACT scores improved (mean 4.1 [5.0]). Similar improvements were seen in adult asthma patients. Modest post-bronchodilator FEV1 improvements (mean [SD], 36 [446] mL) were observed in ACO patients (vs 20 [322] mL in the adult asthma cohort).

Conclusions: In a real-world setting, ACO patients experienced improvements in asthma exacerbations and control and improved FEV1 despite an expected decline after 12 months of omalizumab initiation.

Funding: Genentech, Inc.

Determinants of lung function decline in children and adolescents with severe asthma

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Introduction: This study examined lung function decline factors in adolescents and children with severe asthma from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study.

Methods: Children (6–11 years;n=637) and adolescents (12–17 years;n=627) with severe asthma were analyzed. Baseline lung function and changes from baseline at 12/24 months were compared by sex, white/non-white race, obesity (BMI ≥95%), and exacerbation history.

Results: Children: Females were more likely to be hospitalized but males had slightly lower baseline pre-bronchodilator (BD) FEV_1/FVC. Non-white children were more likely to have urban residence, higher BMI, longer asthma duration, greater exacerbation frequency, and lower pre-/post-BD FEV_1/FVC % at baseline, 12, and 24 months. Obese children had ~2-fold greater hospitalizations and lower FEV_1/FVC%, but higher FVC%. Pre-BD FEV_1 % declined 2% but was not differentiated by any factor.

Adolescents: Sex did not determine exacerbations, lung function, or lung function decline. Non-white adolescents were more likely to be male/obese, have significantly more exacerbations with lower pre-BD FEV_1% and baseline pre-/post-BD FEV_1/FVC%. Obese adolescents were more likely to be non-white, have more exacerbations and higher post-BD FVC%. Pre-BD FEV_1% and FVC% declined from baseline to 24 months by 1.7% and 1.3%, respectively (significantly greater in non-white adolescents). Post-BD FEV_1% and FVC% decline was >4-fold greater in adolescents.

Conclusion: In children with severe asthma, pre-BD FEV_1 declined by ~2% over 2 years but was not informed by sex, race, or obesity. In adolescents with severe asthma, different factors were associated with lung function decline.

Finding Genentech, Inc.

Improvements in asthma-related quality of life observed within 4 weeks of treatment with tezepelumab

Jonathan Corren, Jane R. Parnes, Liangwei Wang, May Mo, Stephanie L. Roseti, Janet M. Griffiths, Sean O'Quinn, René van der Merwe

Rationale: Severe asthma has a major impact on patients' health-related quality of life (HRQOL). We have demonstrated that tezepelumab (AMG 157/MEDI9929), a human monoclonal antibody specific for thymic stromal lymphopoietin, reduced asthma exacerbations and improved Asthma Quality of Life Questionnaire for age ≥12 years [AQLQ(S)+12] overall score vs placebo, in patients with uncontrolled, moderate to severe asthma.[2] Here we further evaluate the effect of tezepelumab on the timing of changes in AQLQ(S)+12 overall and sub-domain scores.

Methods: Patients aged 18–75 years, with uncontrolled asthma, despite inhaled corticosteroid and long-acting beta agonist therapy, were randomized 1:1:1:1 to subcutaneous tezepelumab (70 mg every 4 weeks [low dose], 210 mg every 4 weeks [medium dose], 280 mg every 2 weeks [high dose]) or placebo in a Phase 2 study (NCT02054130).[2] AQLQ(S)+12 was evaluated every 4 weeks (score range: 1–7; increase in value indicates improvement; minimal clinically important difference: 0.5)[2] using a patient self-assessment questionnaire. Nominal *p*-values without multiplicity adjustment are reported for treatment comparisons.

Results: In total, 550 patients were randomized to tezepelumab or placebo. At baseline, patients receiving low-, medium-, high-dose tezepelumab or placebo had mean (standard deviation) AQLQ(S)+12 overall scores of 4.17 (0.93), 4.20 (0.91), 4.08 (0.91) or 4.09 (0.87), respectively. Nominally significant improvements from baseline in AQLQ(S)+12 overall scores were observed as early as Week 4 and Week 8 for patients receiving medium- and high-dose tezepelumab, respectively, when compared with placebo ($p<0.05$). At Week 48, medium- and high-dose tezepelumab treatment improved all AQLQ(S)+12 sub-domain scores (symptoms, activity limitations, emotional function and environmental stimuli) and overall score vs placebo. The percentage of patients who achieved improvements ≥0.5 from baseline in AQLQ(S)+12 overall score at Week 48 was 71.8% (n=79, $p=0.217$) for low-, 76.3% (n=74, $p=0.046$) for medium- and 76.8% (n=76, $p=0.046$) for high-dose tezepelumab, vs 63.8% (n=67) for placebo. Overall, 74.8% (n=229) of patients receiving tezepelumab achieved improvements ≥0.5 from baseline vs 63.8% (n=67) of patients receiving placebo ($p=0.034$) at Week 48.

Conclusion: Medium- and high-dose tezepelumab produced nominally significant improvements from baseline in AQLQ(S)+12 overall score as early as Week 4 and Week 8, respectively. Nominally significant improvements from baseline in all sub-domain scores were observed at Week 48 vs placebo. A greater percentage of tezepelumab-treated patients achieved a clinically meaningful improvement in AQLQ(S)+12 overall score at Week 48 compared with placebo. These HRQOL improvements support the efficacy of tezepelumab in patients with moderate to severe uncontrolled asthma.

Funded by: AstraZeneca

Demographics, clinical characteristics, and response to benralizumab treatment for patients with severe, eosinophilic asthma and fixed airflow obstruction

Chipps BE, Hirsch I, Trudo F, Alacqua M, Zangrilli JG

Introduction: Fixed airflow obstruction (FAO) is frequently associated with the severe eosinophilic asthma phenotype. Benralizumab, a humanized, afucosylated, anti–interleukin-5 receptor alpha monoclonal antibody, reduces exacerbations and improves lung function and daily symptoms in patients with severe, uncontrolled eosinophilic asthma. We assessed the influence of FAO on the response to benralizumab.

Methods: *Post-hoc* analysis of pooled data from the Phase III SIROCCO (48 weeks; *Lancet* 2016;388:2115–27) and CALIMA (56 weeks; *Lancet* 2016;388:2128–41) trials. Patients with severe, uncontrolled asthma aged ≥12 years with baseline blood eosinophils ≥300 cells/μL who were taking high-dosage inhaled corticosteroids and long-acting β_2-agonists received benralizumab 30 mg SC every 4 weeks (Q4W, n=503) or every 8 weeks (Q8W, first three doses Q4W; n=490) or placebo (n=496). FAO was defined by a ratio of postbronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) of <70%. FAO-positive (FAO+) and FAO-negative (FAO–) patients were identified during screening. Demographics, baseline clinical characteristics, and responses to treatment were evaluated by FAO status.

Results: FAO prevalence in the total study population was 63% (935/1,493 patients). At baseline, patients who were FAO+ vs. FAO– were older (mean age [standard deviation {SD}]: 51.3 [12.5] vs. 44.7 [14.9] years), had a longer median (range) time since asthma diagnosis (16.8 [1.1–69.9] vs. 13.3 [1.1–64.0] years), and had a greater percentage of current OCS use (16.0% vs. 9.3%). More FAO+ than FAO– patients were former smokers (24.4% vs. 14.5%). Blood eosinophil counts (median [range]: 510 [300–4,494] vs. 490 [300–3,100] cells/μL) and prior hospitalizations for asthma (23.3% vs. 18.5%) were slightly greater for patients who were FAO+ vs. FAO–. The background exacerbation rate in placebo treated patients was 1.32 vs. 0.86 for FAO+ vs FAO–. For the Q8W regimen, reduction in overall annual asthma exacerbation rate vs. placebo was similar between FAO+ and FAO– cohorts. Greater reductions for FAO+ vs. FAO– were observed for those events associated with a hospitalization or emergency room visit. Improvements in prebronchodilator FEV_1, patient-reported outcomes, and symptoms were consistently greater for patients who were FAO+ vs. FAO–. A similar pattern of efficacy was evident in the Q4W cohort.

Conclusions: FAO was common in patients with severe eosinophilic asthma. Patients with FAO were older and had more severe baseline disease. Add-on benralizumab treatment improved asthma control across several measures for patients with severe eosinophilic asthma and FAO.

Funded by: AstraZeneca

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Benralizumab improves morning peak expiratory flow while reducing oral corticosteroid dosages for patients with severe, uncontrolled asthma in the ZONDA Phase III Trial

Njira L. Lugogo, Joel N. Kline, Ian Hirsch, Mitchell Goldman, James G. Zangrilli, Frank Trudo

Introduction: Add-on oral corticosteroid (OCS) treatment is used to manage symptoms of patients who have uncontrolled asthma despite receiving high-dosage inhaled corticosteroids plus long-acting β_2-agonists (ICS/LABA). However, frequent OCS use is associated with adverse effects. Benralizumab is a humanized, afucosylated anti–interleukin-5 receptor α monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils. In the ZONDA Phase III trial of patients with severe, uncontrolled asthma (NCT02075255; Nair et al. *N Engl J Med*. 2017:376:2248–58), benralizumab significantly reduced OCS dosages from baseline by 75% vs. 25% for placebo (p<0.001), while reducing the annual exacerbation rate by as much as 70% vs. placebo (p<0.001). Here we evaluate the impact of benralizumab treatment and reduced OCS use on lung function, as assessed by peak expiratory flow (PEF), for patients in the ZONDA trial.

Methods: The ZONDA trial included patients (aged 18–75 years) with severe, uncontrolled asthma (eosinophil counts ≥150 cells/μL) who were receiving high-dosage ICS/LABA and had OCS titrated to the minimum effective dosage (baseline) without losing asthma control. Patients received benralizumab 30 mg subcutaneously (SC) either every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses Q4W), or placebo Q4W, for 28 weeks. The treatment period comprised a 4-week induction phase (optimized OCS dosage maintained), a 20-week reduction phase (OCS dosage reduced), and a final 4-week maintenance phase (no further OCS dosage adjustment). In this prespecified analysis, PEF averages over 2-week periods for 28 weeks were estimated. Changes in morning PEF from baseline to Week 28 were analyzed with a repeated measures analysis using the full analysis set.

Results: A total of 220 patients (Q4W, n=72; Q8W, n=73; placebo, n=75) were randomized and received treatment. Morning PEF increases, expressed as least squares mean changes from baseline to Week 28, were greater with benralizumab Q8W than with placebo (difference: 30.01 L/min, nominal p=0.023). Morning PEF increases from baseline to Week 28 were observed also with benralizumab Q4W. These increases were greater than those observed with placebo, but smaller than those observed with benralizumab Q8W. Greater increases in least squares mean changes from baseline in morning PEF with benralizumab Q4W or Q8W vs. placebo were observed during the first 2 weeks (Q8W: difference: 18.73 L/min, nominal p=0.015). Improvements were maintained through Week 28.

Conclusions: As an OCS-sparing therapy, benralizumab improved lung function as assessed by PEF for patients with severe, uncontrolled eosinophilic asthma.

Funded by: AstraZeneca

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Comprehensive asthma management in the primary care setting improves asthma outcomes

Kate Krueck, William Long and Susan Mills

Introduction: Though complications of asthma are largely preventable, implementation of the necessary components of asthma management in the primary care setting is difficult. By observing the effect of interventions aimed at improving asthma assessment and control on Emergency Department (ED) visit and hospital admission rates, we aimed to show that primary care-based comprehensive asthma management can improve asthma outcomes.

Methods: Over a 10 year period, we studied a variety of interventions to improve asthma assessment and management in our large primary care pediatric practice. We adopted those that proved to be both practicable and useful. Sustainable interventions for management of asthma included:

- ☐In-office pulmonary function testing
- ☐Fractional excretion of nitric oxide
- ☐Asthma control test
- ☐Provider assessment and documentation of asthma severity and level of control
- ☐Electronic health records tools including clinical decision support and recall/reminder systems
- ☐Patient education interventions including individualized asthma action plans and resources for ED avoidance

During this time period we measured ED visits and hospital admissions attributable to asthma in order to assess the impact of our interventions on asthma outcomes.

Results: Interventions aimed at improving asthma management resulted in a reduction in asthma related ED initial and repeat visits and hospital admissions for patients in our primary care practice.

Conclusions: Implementation of a comprehensive asthma management program resulted in improved outcomes for patients with asthma in our primary care practice. Improvement in asthma related ED visits and hospital admissions are known factors in reducing health care costs and improving quality of life measures.

Pediatric Associates, Inc. of Columbus Ohio

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Use of the knowledge-to-action framework to advance physician learning and behaviors surrounding personalized precision asthma care

Siddhartha Singh, Shyam Subramanian, Ileen Gilbert, Sue McGuinness, Salim Surani

Introduction: Recent advances in immunobiology have led to a paradigm shift in the management approach for patients with severe asthma, emphasizing personalized, precision care. This, in turn, creates challenges of translating the rapidly evolving science, and evidence-based guidelines, into health interventions to affect physician behavior in a timely, effective, and efficient manner. Knowledge, administrative, and value proposition barriers may prevent translation of evidence into practice and explain why guidelines for all diseases are implemented <60% of the time. The US AstraZeneca PRECISION initiative aims to positively influence physician behavior toward appropriately diagnosing/managing patients with severe asthma via employing the Knowledge-to-Action framework — a model consisting of Knowledge Creation and Action Cycle components. As the first step of the Action Cycle, we wanted to quantify the current state of clinical practice surrounding severe asthma.

Methods: An online quantitative survey was completed by pulmonary practitioners in the relevant CHEST Networks and attendees at the 2017 ATS annual meeting (May 2017, Washington, DC). Four multi-component questions addressed challenges (4 items), resources (4), practice patterns (14), and education preferences (8) surrounding diagnosis/management of severe asthma. Respondents were classified by practice setting: academic medical center (AMC) vs community-based (CB).

Results: 120 providers (AMC=48; CB=72) formed the basis of this interim analysis. One-third managed ≥50 patients with severe asthma and one-fifth of these patients were treated with biologics. The majority of respondents endorsed the following resources as necessary to manage severe asthma: information on new diagnostic/therapeutic options (85%), practice team members to facilitate access to therapies (83%) and educate patients (83%), and a physical environment for patients to receive injections (89%). However, many reported lacking access to these resources (25%, 33%, 36%, and 14%, respectively, for each). The degree to which respondents considered various clinical parameters when making management decisions varied by practice setting, with CB versus AMC-based providers placing greater importance on biomarkers (IgE, serum eosinophils, FeNO) and less upon objective symptom measures (ACT, ACQ). Overall, virtual education was desired at least as much as face-to-face opportunities.

Conclusions: These data form a first step in identifying Action Cycle barriers affecting diagnosis/management of patients with severe asthma. The US AstraZeneca PRECISION initiative will integrate these findings with direct insights from practitioners in geographic regions with the greatest patient morbidity, to inform the Knowledge Creation component and development of unique tools and educational materials to advance the adoption of personalized/precision care for severe asthma.

Funded by: AstraZeneca

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Impact of body mass index on efficacy of benralizumab in patients with severe, uncontrolled eosinophilic asthma: pooled analysis of the SIROCCO and CALIMA Trials

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Introduction: Obesity is associated with increased asthma severity and poor control (*Respirology*. 2017;22:651–61). Benralizumab is a humanized, afucosylated, anti–interleukin-5 receptor α monoclonal antibody that directly and rapidly depletes eosinophils, reduces exacerbations, and improves daily symptoms for patients with severe, uncontrolled eosinophilic asthma. We evaluated the impact of body mass index (BMI) on the efficacy of benralizumab.**Methods:** We conducted a *post-hoc* pooled analysis of the Phase III SIROCCO (48 weeks; *Lancet*. 2016;388:2115–27) and CALIMA (56 weeks; *Lancet*. 2016;388:2128–41) trials. Patients aged ≥12 years on high-dosage inhaled corticosteroids/long-acting β_2-agonists with baseline blood eosinophils ≥300 cells/μL (full analysis set) received benralizumab 30 mg subcutaneously either every 4 weeks (Q4W, n=503) or every 8 weeks (Q8W, first three doses Q4W; n=490), or placebo (n=496). This *post-hoc* analysis of adult patients (aged ≥18 years) categorized patients as normal/underweight (BMI <25 kg/m^2), overweight (BMI ≥25–<30 kg/m^2), or obese (BMI ≥30 kg/m^2). Efficacy outcomes included annual exacerbation rate and change from baseline to end of treatment in prebronchodilator forced expiratory volume in 1 second (FEV_1) by BMI categories.

Results: Baseline demographics and clinical characteristics of age, lung function, smoking history, and oral corticosteroid use were similar across all treatment and BMI groups. There was a trend toward lower baseline eosinophil counts with increasing BMI. Improvements in exacerbation rates and lung function were similar between the Q4W and Q8W cohorts relative to placebo for the respective BMI groups. Benralizumab treatment was associated with improvements in exacerbation rates vs. placebo for the normal/underweight and overweight groups (e.g., Q8W, rate ratio 0.51 and 0.43, respectively, nominal $p \leq 0.0003$), and numerical improvements were observed with benralizumab (both dosages) vs. with placebo for the obese group. Increases in prebronchodilator FEV_1 from baseline were greater with benralizumab treatment vs. with placebo for the normal/underweight and overweight groups (e.g., Q8W: 0.148 and 0.214 L, respectively, nominal $p \leq 0.0199$), and numerical improvements were seen with benralizumab (both dosages) vs. with placebo for the obese group.

Conclusions: For patients with severe, uncontrolled eosinophilic asthma, benralizumab decreased asthma exacerbations and increased lung function regardless of BMI value. For patients with severe asthma and comorbid obesity, asthma exacerbation rate reductions and prebronchodilator FEV_1 improvements numerically favored benralizumab. Improvements, particularly in FEV_1, were less robust for obese patients.

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What symptomatic patients with asthma and chronic obstructive pulmonary disease (COPD) find important in their maintenance inhaler therapy: A focus group study

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Introduction: Inhaled corticosteroids (ICS), long-acting beta agonists (LABA), and long-acting muscarinic antagonists (LAMA) combination therapies are standard maintenance treatments for asthma and COPD. This study evaluated which treatment attributes asthma and COPD patients value most in their inhaled maintenance therapies.

Methods: Five patient focus groups (N=37) were conducted in 2 US cities: 2 asthma patient groups (N=15; mean Asthma Control Questionnaire (ACQ) score=2.0, SD=1.3) and 3 COPD patient groups (N=22; COPD Assessment Test (CAT) score >10, mean=28.6, SD=6.0) on ICS/LABA, LAMA/LABA, or ICS/LABA+LAMA maintenance therapies. Participants described important attributes of their maintenance treatment(s) and ranked ≤5 most important treatment attributes. Focus group transcripts were analyzed using qualitative content analysis, and the ranked attribute responses were categorized.

Results: Most participants were female (68%) and had employer-provided health insurance (62%); mean age was 52.4 years. Treatment effectiveness (eg, decrease in exacerbation frequency, reduced rescue medication use) was the most important attribute for patients, but COPD patients included more effectiveness attributes in their rankings than asthma patients. Inhaler device convenience (eg, number of priming steps, easy-to-read dose counter), side effects (eg, weight gain), dosing frequency, cost, and taste (eg, taste of drug capsule particles) were also ranked as important attributes. Although most patients (97%) had health insurance, out-of-pocket costs were a concern across groups; some patients reported being non-adherent for cost reasons.

Conclusions: Although effective symptom management is the key maintenance therapy attribute for asthma and COPD patients, non-clinical attributes such as convenience and costs are also important and can affect treatment adherence.

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Differences in healthcare resource use and costs between post-discharge chronic obstructive pulmonary disease patients treated with dry-powder inhalers and pressurized metered-dose inhalers

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Introduction: The primary treatment for chronic obstructive pulmonary disease (COPD) is medication administered via dry-powder inhalers (DPIs) or pressurized metered-dose inhalers (pMDIs). This study examined real-world differences in healthcare resource use (HRU) and costs among COPD patients treated with a DPI or pMDI ≤10 days post-discharge for a COPD exacerbation.

Methods: This retrospective database analysis included COPD patients aged ≥40 years with an inpatient admission for COPD exacerbation who received a prescription on the index date for a DPI or pMDI inhaled corticosteroid/long-acting beta-agonist (ICS/LABA) combination and had continuous enrollment for 12 months pre- (baseline) and 90 days post-index date. Outcomes included baseline and post-index HRU and costs.

Results: There were 1960 DPI and 1086 pMDI initiators. During the pre-index period, the pMDI group was significantly more likely to use short-acting beta agonists, experienced more COPD hospital days, and had more pulmonologist visits versus DPI (all $p<0.05$). Thirty-day post-index all-cause readmissions were similar between groups. During follow-up, the pMDI group had significantly lower all-cause total outpatient costs, COPD-related total medical costs, and COPD-related total healthcare costs, and were less likely to fill tiotropium prescriptions within 30 days following ICS/LABA initiation (all $p<0.05$).

Conclusions: The pMDI group demonstrated elevated COPD-related baseline HRU and costs versus DPI. Despite similar readmission rates as DPI, pMDI use was associated with significantly lower all-cause outpatient costs, and significantly lower COPD-related outpatient, medical, and total healthcare costs, suggesting that COPD patients may experience reduced healthcare burden when taking inhaled ICS/LABA via pMDI versus DPI.

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The effect of season on hospitalization and mortality in patients with idiopathic pulmonary fibrosis treated with pirfenidone versus placebo

Brett Ley, Rishi Raj, Benjamin Trzaskoma, Elizabeth Morgenthien, John L. Stauffer, Susan L. Limb, Jeffrey J. Swigris

Rationale: Chronic lung diseases often have a seasonal pattern of disease activity. Data from the pivotal studies of pirfenidone were analyzed to assess the impact of season on hospitalization and mortality in patients with idiopathic pulmonary fibrosis (IPF).

Methods: Patients randomized to pirfenidone 2403 mg/day or placebo in ASCEND (NCT01366209) or CAPACITY (NCT00287729 and NCT00287716) were analyzed for the following events over 12 months: respiratory-related hospitalization, non–respiratory-related hospitalization and a composite endpoint of respiratory-related hospitalization or death from any cause. Each hospitalization or death date was assigned to Spring, Summer, Fall or Winter (starting on March, June, September or December 22nd, respectively). Within each treatment group, a repeated-measures analysis for correlated binary data tested for a trend across the seasons.

Results: In the placebo arm (n=623), a seasonal trend was observed in the proportion of patients with respiratory hospitalizations (P=0.035) and the composite endpoint (P=0.026) but not the pirfenidone arm (P=0.484 and P=0.144, respectively). In Winter (but not other seasons), a significantly greater proportion of patients in the placebo vs. pirfenidone arm had a respiratory hospitalization (4.4% vs. 2.3%; P=0.037, Chi-squared test). Season did not appear to affect non-respiratory hospitalizations in either treatment arm (P=0.406 and P=0.509, respectively)

Conclusions: In patients with IPF who received placebo in ASCEND and CAPACITY, more respiratory hospitalizations and greater all-cause mortality were observed in Fall and Winter vs. Spring and Summer. Pirfenidone appeared to blunt seasonal peaks in respiratory hospitalizations. No seasonal trend was observed for non-respiratory hospitalizations.

Funding: Genentech, Inc.

Physician characteristics associated with treatment initiation patterns in idiopathic pulmonary fibrosis: Results from an online, self-administered survey

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Rationale: Physician-specific factors may play a role in determining idiopathic pulmonary fibrosis (IPF) treatment. This analysis described physician characteristics associated with different approaches to antifibrotic treatment initiation following an IPF diagnosis.

Methods: An online, self-administered survey was fielded to US pulmonologists between April 10 and May 17, 2017. Eligible participants spent >20% of their time in direct patient care and had ≥5 patients with IPF receiving antifibrotics. Participants answered questions regarding practices, attitudes and decision-making for initiating antifibrotics post-IPF diagnosis. Participants were categorized by willingness to consider initiating antifibrotic therapy immediately after IPF diagnosis ("yes, all the time/most of the time" [considerers of immediate initiation] vs. "only some of the time/no, usually not").

Results: Of pulmonologists surveyed (N=169), 81.7% were considerers of immediate initiation of antifibrotics; 18.3% were not. Considerers of immediate initiation were more likely to work in private practice (26.1% vs. 16.1%), have more patients currently receiving antifibrotics (60.8% vs. 30.5%) and make treatment initiation decisions themselves (31.2% vs. 16.1%). Pulmonary function test results (87.5%), symptom severity (79.2%), patient request (73.8%) and radiological findings (72.6%) were common reasons for immediate antifibrotic initiation in both groups. On average, a "watch-and-wait" approach was reported for 32.7% of newly diagnosed patients; the main reasons were patient preference (86.3%), absence of symptoms (79.7%) and minimal pulmonary function test abnormalities (72.5%).

Conclusions: Most pulmonologists consider immediate initiation of antifibrotics, although practice setting, percent of patients receiving antifibrotics and patient-physician decision-making dynamics were distinguishing characteristics for treating immediately vs. "watch-and-wait."

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Comparison of PEF vs. FEV_1 endpoints in trials with tiotropium in adults and adolescents with moderate or severe symptomatic asthma

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Introduction: In asthma clinical trials involving adults and adolescents, forced expiratory volume in 1 second (FEV_1) is generally preferred for lung function assessment, while peak expiratory flow (PEF) represents an alternative endpoint.

Methods: FEV_1 and PEF outcomes from 5 trials with tiotropium-Respimat® add-on to ICS±other controllers were compared. Change from baseline in peak $FEV_{1(0–3h)}$, trough FEV_1, and $PEF_{am/pm}$ with tiotropium 5µg, 2.5µg, and placebo delivered by Respimat® (2 puffs once daily) were analyzed from studies in patients with symptomatic asthma (adults: GraziaTinA-asthma® and MezzoTinA-asthma®; 12–17-year-olds: PensieTinA-asthma® and RubaTinA-asthma®). However, only 2.5µg, the U.S.-approved dose is discussed here. Correlation of in-clinic and weekly mean home measurements (AM3® Home Spirometer and eDiary) of FEV_1 and PEF was also analyzed *post hoc*.

Results: Improvements in lung function were seen in all studies with tiotropium-Respimat®. Absolute change from baseline (ml) in peak $FEV_{1(0–3h)}$, trough FEV_1, and PEF_{am} are reported- GraziaTinA-asthma®: 159, 110, 26.3; MezzoTinA-asthma®: 223, 180, 25.4; PensieTinA-asthma®: 111, 115, 10.5; RubaTinA-asthma®: 134, 84, 9.7. At-home versus in-clinic measurements correlated better for PEF (intra-class correlation coefficient [ICC] 0.724–0.839) than for FEV_1 (ICC 0.575–0.818), at Week 12 or 24, depending on the study, indicating that home-assessed PEF as an endpoint may give additional information over FEV_1.

Conclusion: FEV_1 and PEF both improved with tiotropium added to ICS±other controllers versus placebo in all studies. However, home PEF measurements may have certain advantages over home FEV_1 measurements such as ease of use and increasing convenience for the study subject.

Funding: Boehringer Ingelheim

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Exacerbation history and eosinophil count are predictors of outcomes following ICS withdrawal in COPD

Henrik Watz, Kay Tetzlaff, Achim Mueller, Helgo Magnussen, Peter Calverley

Introduction: Exacerbation history and eosinophil count may predict response to inhaled corticosteroids (ICS) in COPD. In this study, we investigated whether the presence of these factors at baseline predicted time to first exacerbation with ICS withdrawal in the Withdrawal of Inhaled Steroids during Optimized bronchodilator Management (WISDOM) study.

Methods: This is a post hoc subgroup analysis of WISDOM, a 12-month, double-blind, parallel-group study in which patients received tiotropium (18 µg once daily), salmeterol
(50 µg twice daily) and fluticasone propionate (500 µg twice daily) for 6 weeks before randomization (1:1) to either continue all treatments or stepwise withdrawal of fluticasone propionate over 12 weeks. Of the 2485 patients randomized in the WISDOM study, 2419 were included in this analysis.

Results: Exacerbation history alone did not identify patients who were susceptible to increased exacerbations with ICS withdrawal ($p = 0.2854$). However, among patients with eosinophil count ≥400 cells/µL ($n = 270$), those with ≥2 exacerbations in the year before randomization ($n = 51$) had a higher risk of moderate or severe exacerbation with ICS withdrawal than the other subgroups (≥2 exacerbations and without ICS withdrawal [$n = 46$]; <2 exacerbations and with or without ICS withdrawal [$n = 89$ and 84, respectively]).

Conclusions: In this subgroup analysis, both eosinophil count and exacerbation history appeared to be predictive of patients with severe to very severe COPD, thus identifying a small subpopulation of patients that are at increased risk of exacerbation after ICS withdrawal and who will benefit from ICS continuation.

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Omalizumab: More than 15 years of health impact in asthma

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Introduction: Omalizumab, a monoclonal antibody (mAb) against immunoglobulin E (anti-IgE) was the first biologic developed for the treatment of moderate and severe allergic asthma (SAA). More than 970'000 patients-years are estimated to have been exposed to omalizumab since its first registration: Australia, 2002 (Periodic Safety Update Report). This analysis estimates the contribution of omalizumab in reducing asthma burden over 15 years.

Methods: A model was built to estimate impact of omalizumab on asthma-related health outcomes: deaths, exacerbations, improvement in quality adjusted life years (QALYs) and days with improved symptoms. Cumulative asthma deaths avoided were calculated by applying published asthma-related mortality risks on exacerbations leading to: (i) hospitalization (ii) hospitalization or ED visit. Number of exacerbations, ED visits and hospitalizations were retrieved from INNOVATE, a randomized clinical trial.

Results: Between 367 and 915 deaths due to asthma and 78-128'000 exacerbations leading to ED or hospitalizations are estimated to have been avoided depending on responder scenario; 40 days of improved symptoms and an average of one year and one month of full health (+1.08 years in QALYs) were gained per patient treated

Conclusions: On average, each patient responding to omalizumab gained 1 year and 1 month of full health. Omalizumab reduced asthma deaths by 58% in secondary care. Continuous effort is necessary from all stakeholders to link access to effective treatments to appropriate disease management. Data for asthma mortality risk outside secondary care is warranted.

Funding: Novartis

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A randomized, double-blind, placebo controlled, multicenter phase 2a study to assess safety and daily respiratory symptoms after administration of either ypl-001, a botanical drug product, or placebo in patients with moderate to severe chronic obstructive pulmonary disease

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Introduction: This study was designed to reveal evidence of favorable or adverse effects of YPL-001 in patients with moderate to severe chronic obstructive pulmonary disease (COPD; GOLDS 2-3).

Methods: Following a 2-week run-in period, 61 patients were randomized to receive either 80 mg YPL-001, 160 mg YPL-001, or placebo oral doses twice daily (BID) for 8 weeks. Safety assessments were performed throughout the study. Assessment of respiratory symptoms was performed daily through patient-reported outcomes of peak expiratory flow (PEF), major (estimated sputum quality and quantity) and minor symptoms (cough, wheeze, sore throat, nasal congestion, nasal discharge, and body temperature > 100°F) of COPD exacerbation, dyspnea, and activity. Spirometry measurements and quality of life assessments were performed bi-weekly.

Results: Fewer patients reported AEs following YPL-001 160 mg (38%) and 80 mg (50%) than placebo (70%) with no discernable treatment- or time-related trends in other safety assessments. Common AEs were COPD exacerbation and cough, with the majority reported in patients receiving placebo. There was a dose-related reduction in the percentage of COPD patients with weekly mean COPD symptom scores ≥ 2 and a 30 L/min increase in mean daily PEF values in patients receiving YPL-001 compared to placebo. There were no discernable differences in other reported outcomes and spirometry results except for a small increase in inspiratory capacity in YPL-001 treatment groups compared to placebo.

Conclusions: Oral doses of YPL-001 are safe and well tolerated in patients with moderate to severe COPD. YPL-001 may reduce respiratory exacerbations associated with COPD by improving maximum ventilatory capacity.

Funding: Celerion

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Lung function and patient-reported outcomes response to glycopyrrolate (SEEBRI™ Neohaler®) in chronic obstructive pulmonary disease (COPD) patients by reversibility: pooled analysis of the GEM1 and GEM2 studies

Alyssa Bowling, Thomas Goodin, Barry Price, Ayca Ozol-Godfrey, Sanjay Sharma, Shahin Sanjar, Jill Ohar

Rationale: Bronchodilator reversibility is a key characteristic of asthma but is also present in COPD. The impact of reversibility on lung function, health status, and dyspnea was assessed in COPD patients treated with glycopyrrolate (GLY) 15.6 mcg twice daily versus placebo.

Methods: GEM1 (NCT01709864) and GEM2 (NCT01715298) were replicate, 12-week, multicenter, double-blind, placebo-controlled studies that randomized patients (1:1) with moderate-to-severe COPD to receive GLY or placebo. Patients with a history of asthma were excluded. A pooled analysis of the 873 randomized patients compared GLY versus placebo by reversibility for the following endpoints: forced expiratory volume in one second area under the curve from 0–12 hours (FEV_1 $AUC_{0–12h}$; L), St. George's Respiratory Questionnaire (SGRQ) total score, and Transition Dyspnea Index (TDI) focal score. FEV_1 reversibility was calculated as percentage increase of FEV_1 after inhalation of a bronchodilator, compared to FEV_1 before bronchodilator inhalation. Reversibility was defined as a post-bronchodilator increase of ≥12% and ≥0.200 L in FEV_1.

Results: In the pooled analysis (N=873), the overall mean (standard deviation) reversibility was 20.3% (16.3%) and 47.9% of patients met the reversibility criteria. GLY showed statistically significant improvements in FEV_1 $AUC_{0–12h}$ at Day 85 compared to placebo, regardless of reversibility status (least squares mean treatment difference: reversible 0.154 L, p<0.001; non-reversible 0.112 L, p<0.001). Significant reductions in SGRQ total score versus placebo were observed, with smaller reductions in the reversible group compared to non-reversible group (–3.5, p=0.004; –4.8, p<0.001). Significant increases in TDI focal score compared to placebo were seen in the reversible group (1.03, p<0.001), however increases in the non-reversible group were not significant (0.2, p=0.512).

Conclusion: In this pooled analysis, GLY demonstrated significant improvements in lung function and SGRQ total score compared to placebo, regardless of reversibility status. The effect of reversibility on the response to bronchodilator therapy should be explored in future studies.

Funding: Sunovion

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Cardiovascular safety and efficacy of nebulized glycopyrrolate/eflow cs in phase 3 trials of patients with moderate to very severe COPD

Gary Ferguson, Robert Tosiello, Thomas Goodin

Rationale: The GOLDEN Phase 3 studies in subjects with moderate-to-very-severe COPD assessed the efficacy and safety of a novel, nebulized glycopyrrolate (GLY) and were prospectively designed to include subjects with cardiovascular (CV) risk factors.

Methods: In two 12-week and one 48-week study, 2379 subjects were stratified by CV risk (high vs low) and randomized to placebo, GLY 25 or 50 mcg twice daily, or tiotropium (TIO; 18 mcg once daily). Safety, lung function, patient-reported outcomes and exacerbations were assessed by CV risk subgroup.

Results: Across studies, 1526 subjects were at high CV risk and 853 were at low CV risk. At week 12, the incidence of adverse events leading to discontinuation was similar in high and low CV risk subgroups and lower in GLY 25 and 50 mcg groups (high: 6.2% and 3.6%; low: 3.2% and 4.5%) than placebo (high: 9.0%; low: 9.9%). In the 48-week study, discontinuations were higher for GLY (high: 10.7%; low: 8.7%) vs TIO (3.7%; 1.2%, respectively), partly due to increased cough and COPD event rates. CV events of special interest were low in both CV risk subgroups, and generally similar between treatments at 12 weeks (high: placebo, 3.6%; GLY 25 mcg, 1.1%; GLY 50 mcg, 2.2%; low: 0.7%; 2.6%; 1.9%, respectively). Incidences at 48 weeks were similar in the high CV risk group and numerically higher for TIO than GLY in the low CV risk subgroup, particularly for arrhythmias (high: GLY, 5.0%; TIO, 5.1%; low: GLY, 2.3%; TIO, 4.1%). Major adverse cardiac events (MACE) occurred more frequently with placebo in the high CV risk subgroup at 12 weeks (incidence rate [IR] for high vs low: placebo, 25.1 vs 0; GLY 25 mcg, 0 vs 0; GLY 50 mcg, 24.3 vs 21.6). At 48 weeks, IR for MACE were higher for TIO than GLY (high vs low: GLY, 6.7 vs 6.0; TIO 24.3 vs 13.6). GLY led to statistically significant, clinically important improvements in trough forced expiratory volume in 1 second (FEV1) in high and low CV risk subgroups at week 12 vs placebo (25 mcg, 95 and 97 mL; 50 mcg, 99 and 113 mL, respectively, p<0.001). The overall change from baseline in trough FEV1 was similar across CV risk subgroups for GLY (100 and 94 mL) and TIO (84 and 107 mL) over 48 weeks' treatment. At week 12, in both subgroups, GLY produced statistically significant improvements (p<0.05) vs placebo in St George's Respiratory Questionnaire (SGRQ) and the proportion of GLY responders was consistently higher than placebo. Over 48 weeks, change from baseline in SGRQ was higher for GLY vs TIO in the high CV risk subgroup, as was the proportion of GLY SGRQ responders at 48 weeks (47% vs 39%). Change and response for the low risk group was numerically higher for TIO than GLY. Exacerbation rates were similar across all treatment groups and most exacerbations were moderate in severity in both subgroups after 12 and 48 weeks.

Conclusion: Nebulized GLY had an acceptable safety/tolerability profile and improved lung function and patient-reported outcomes in subjects with COPD and CV risk factors for up to 48 weeks.

Funding: Sunovion

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The effect of concurrent bronchodilator therapy on the efficacy and safety of a novel, nebulized glycopyrrolate in phase 3 studies in subjects with moderate to very severe COPD

Edward Kerwin, Robert Tosiello, Barry Price, Thomas Goodin

Rationale: The GOLDEN Phase 3 studies assessed the efficacy and safety of a novel, nebulized glycopyrrolate (GLY) for up to 48 weeks, and included subjects on stable doses of long-acting β2-agonists (LABA) ± inhaled corticosteroids (ICS) who continued background therapy over the treatment period.

Methods: In two 12-week placebo-controlled studies and one 48-week active-controlled study, 2379 subjects were stratified by background LABA±ICS (LABA-yes [n=861] vs LABA-no [n=1518]) and randomized to placebo, GLY 25 or 50 mcg twice daily (BID) via an investigational eFlow Closed System nebulizer (PARI Pharma, Germany), or tiotropium (TIO; 18 mcg once daily). Lung function, patient-reported outcomes, exacerbations and safety were assessed in the LABA subgroups. Statistical methodology included mixed-model repeated measures, analysis of covariance and descriptive safety data.

Results: GLY 25 and 50 mcg BID produced statistically significant and clinically important improvements vs placebo in trough forced expiratory volume in 1 second (FEV_1; 92-110 mL, p<0.001) in LABA subgroups at week 12. The overall change from baseline in trough FEV_1 was similar for GLY 50 mcg BID and TIO (92-106 mL) in both LABA subgroups at week 48. At 12 weeks, GLY produced statistically significant improvements in SGRQ in LABA subgroups (-2.073 to -3.888 vs placebo, p<0.05), and the proportion of SGRQ responders was consistently higher with GLY 25 and 50 mcg BID (LABA-yes: 48.3%, 43.4%; LABA-no: 46.1%, 40.9%) than placebo (yes: 24.8%; no: 38.7%). Over 48 weeks, change from baseline SGRQ in the LABA-yes subgroup was -5.190 for GLY and -3.094 for TIO, and -4.368 and -4.821, respectively, in the LABA-no subgroup. The proportion of GLY SGRQ responders was higher in the LABA-yes (53.7% vs 41.1% TIO) and similar to TIO in the LABA-no (42.6% vs 48.8% TIO) subgroups after 48 weeks. Exacerbation rates were generally similar across treatments and most were moderate in severity in both LABA subgroups after 12 and 48 weeks. The incidence of adverse events leading to discontinuation was similar in the LABA subgroups and less frequent in the GLY groups compared to placebo at 12 weeks. There was a higher discontinuation rate in the GLY LABA subgroups, with higher overall cough and COPD incidence rates (IRs) vs TIO. Cardiovascular events of special interest were more frequent in the LABA-no subgroup with generally similar IRs between treatments in LABA subgroups at 12 and 48 weeks. At 12 weeks, there were two major adverse cardiac events (MACE; IR per thousand patient-years=23.6) in the placebo LABA-no group and three MACE (IR=33.9) in the GLY 50 mcg BID LABA-no group. The MACE IRs in the TIO group were numerically higher than GLY in both LABA subgroups at 48 weeks.

Conclusion: Nebulized GLY improved lung function and patient-reported outcomes with an acceptable safety/tolerability profile in subjects with COPD, with and without background LABA_ICS, for up to 48 weeks.

Funding: Sunovion

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The efficacy and safety of a novel, nebulized glycopyrrolate for the treatment of COPD in phase 3 placebo-controlled studies: Effect of baseline lung function and age

Jill Ohar, Robert Tosiello, Thomas Goodin, Shahin Sanjar

Rationale: A nebulized long-acting muscarinic antagonist (LAMA), glycopyrrolate (GLY), delivered by an investigational eFlow® Closed System (CS) nebulizer (PARI Pharma, Germany), was assessed in two placebo-controlled trials in subjects aged ≥40 years with moderate-to-very-severe COPD. Subgroup analyses were performed based on baseline post-bronchodilator % predicted forced expiratory volume in 1 second (FEV_1 % pred.) and age.

Methods: In two 12-week studies (n=1294; 31% on background long-acting β2-agonist ± inhaled corticosteroid), lung function, health status, exacerbations and safety were assessed in subgroups: FEV_1 % pred <50% and ≥50%; and age <65, ≥65, and ≥75 years. Statistical methodology included mixed-model repeated measures, analysis of covariance and descriptive safety data.

Results: At week 12, GLY (25 and 50 mcg twice daily [BID], respectively; n=431, 432) produced significant (p<0.05) and clinically important improvements in trough FEV_1 vs placebo in all subjects (94 and 104 mL) and in FEV_1 % pred <50% (70 and 79 mL; n=185, 193) and ≥50% (112 and 126 mL; n=245, 239) groups. Both GLY doses produced significant (p<0.05), clinically important lung function improvements vs placebo in subjects aged <65 years (56 and 86 mL; n=231, 254), ≥65 years (140 and 124 mL; n=200, 178), and ≥75 years (144 and 120 mL; n=47, 38). Both GLY doses led to significant (p<0.05) improvements in St George's Respiratory Questionnaire (SGRQ) total score in all subjects (-3.346 and -2.714) vs placebo and in the FEV_1 % pred <50% (-3.237 and -3.061) and ≥50% (-3.392 and -2.322) groups. Overall, and in the lung function subgroups, a higher proportion of SGRQ responders was seen with both GLY doses (all: 46.8% and 41.7%; <50%: 44.6% and 45.9%; ≥50%: 48.1% and 38.1%) vs placebo (all: 34.5%; <50%: 32.4%; ≥50%: 35.9%). SGRQ improvements occurred in all age groups, with a higher percentage of GLY vs placebo responders. The highest SGRQ improvement (-6.287) was in the ≥75 years subgroup receiving GLY 25 mcg BID (n=47). Exacerbation rates were similar for placebo and GLY doses across subgroups, and most were moderate in severity. The incidence of adverse events (AEs) leading to discontinuation was generally higher with placebo vs GLY across subgroups. Cough, dyspnea, and COPD worsening were the most common AEs leading to discontinuation. Discontinuation for bronchospasm and pneumonia were only observed with placebo. Few cardiovascular events of special interest were seen. Two major adverse cardiac events (MACE) (CV death, non-fatal myocardial infarction [MI]; 50 mcg BID) occurred in the <65 years subgroup and three MACE (2 non-fatal MIs, placebo; non-fatal stroke, 50 mcg BID) in the ≥65 years subgroup.

Conclusion: Nebulized GLY delivered by the eFlow® CS demonstrated improvements in lung function and health status with acceptable safety/tolerability over 12 weeks in subjects with moderate-to-very-severe airflow limitation, including those aged ≥75 years.

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Lung function and patient-reported outcomes response to indacaterol/glycopyrrolate (UTIBRON™ Neohaler®) in chronic obstructive pulmonary disease (COPD) patients by smoking status: Pooled analysis of the FLIGHT1 and FLIGHT2 studies

Shahin Sanjar, Thomas Goodin, Alyssa Bowling, Barry Price, Ayca Ozol-Godfrey, Sanjay Sharma, Donald P Tashkin

Rationale: Smoking is a leading risk factor for the development of COPD. The association between smoking status and long-acting bronchodilator response is not well understood. We explored the relationship between smoking status and clinical outcomes in COPD patients treated with indacaterol/glycopyrrolate 27.5/15.6 mcg (IND/GLY) twice daily versus placebo.

Methods: A pooled analysis of the FLIGHT1 (NCT01727141) and FLIGHT2 (NCT01712516) 12-week, randomized studies in patients with moderate-to-severe COPD was conducted to compare IND/GLY versus placebo grouped by smoking status for the following endpoints: forced expiratory volume in one second area under the curve from 0–12 hours (FEV_1 $AUC_{0–12h}$; L), St. George's Respiratory Questionnaire (SGRQ) total score, and Transition Dyspnea Index (TDI) score.

Results: Of the 2043 randomized patients in this pooled analysis, 51.6% were current smokers while 48.4% were ex-smokers. IND/GLY, when compared to placebo, showed statistically significant improvements in both current and ex-smokers in FEV_1 $AUC_{0–12h}$ at Week 12 (least squares mean treatment difference: current smokers 0.248 L, p<0.001; ex-smokers 0.243 L, p<0.001). Significant reductions in SGRQ total score versus placebo were observed, with greater reductions in the current smokers (–5.9, p<0.001) compared to ex-smokers (–4.2, p<0.001). For the TDI score, significant increases were also seen regardless of smoking status: smokers (1.53, p<0.001); and ex-smokers (1.75, p<0.001).

Conclusion: In this pooled analysis, IND/GLY demonstrated significant improvements compared to placebo in lung function, SGRQ total score, and TDI score regardless of smoking status. While lung function response was similar between current smokers and ex-smokers, there were numerical differences for the SGRQ and TDI. Prospective studies should be done to better understand the impact of smoking status on clinical outcomes in randomized clinical trials.

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Lung function and patient-reported outcomes response to indacaterol/glycopyrrolate (UTIBRON™ Neohaler®) in chronic obstructive pulmonary disease (COPD) patients by reversibility: Pooled analysis of the FLIGHT1 and FLIGHT2 studies

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Rationale: Bronchodilator reversibility is a key characteristic of asthma but is also present in COPD. The impact of reversibility on lung function, health status, and dyspnea was assessed in COPD patients treated with indacaterol/glycopyrrolate (IND/GLY) 27.5/15.6 mcg twice daily versus placebo.

Methods: A pooled analysis of the FLIGHT1 (NCT01727141) and FLIGHT2 (NCT01712516) 12-week, randomized studies in 2043 patients with moderate-to-severe COPD was conducted to compare IND/GLY versus placebo by reversibility for the following endpoints: forced expiratory volume in one second area under the curve from 0–12 hours (FEV_1 $AUC_{0–12h}$; L), St. George's Respiratory Questionnaire (SGRQ) total score, and Transition Dyspnea Index (TDI) score. Any history of asthma was an exclusionary criterion. FEV_1 reversibility was calculated as percentage increase of FEV_1 after sequential inhalation of short-acting (anticholinergic and $beta_2$-agonist) bronchodilators. Reversibility was defined as a post-bronchodilator increase of ≥12% and ≥0.200 L in FEV_1.

Results: The pooled analysis showed that the overall mean (standard deviation) reversibility was 22.8% (17.6%) and 54.5% of patients met the reversibility criteria. IND/GLY showed statistically significant improvements compared to placebo in FEV_1 $AUC_{0–12h}$ at Day 85 regardless of reversibility status (least squares mean treatment difference: reversible 0.308 L, p<0.001; non-reversible 0.170 L, p<0.001). Significant reductions in the SGRQ total score versus placebo were also observed, with greater reductions in the reversible group than in the non-reversible group (–6.3, p<0.001; –3.5, p=0.001). For the TDI score, significant increases compared to placebo were seen in reversible and non-reversible groups with greater improvements in the reversible group (1.93, p<0.001 and 1.29, p<0.001, respectively).

Conclusion: In this pooled analysis, IND/GLY demonstrated significant improvements in lung function, SGRQ total score, and TDI score compared to placebo, regardless of reversibility status, with greater improvements observed in reversible patients. The effect of reversibility on the response to bronchodilator therapy should be explored in future studies.

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