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 ($P_e$) was identified in 36 of 70 (51.4%; 95% CI, 39.2%-63.6%) patients. Twenty-seven of 36 (75%) patients with abnormal $P_e$ demonstrated a biphasic P/V curve (partially expandable lung), while 9 of 36 (25%) demonstrated a monophasic P/V curve with increased $P_e$. Volume loss or post-procedural pleural thorax was uncommon in the abnormal $P_e$ and post-procedural pleural thorax 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.
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, but it can also affect extrapulmonary sites. In young women, it is characterized by cystic lung lesions, 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 surgery for a pelvic mass. The mass consisted of a solid component and cystic areas, which were aspirated for histological analysis. Histological analysis showed a solid infiltrative tumorous mass composed of atypical smooth muscle cells with mucinous cysts. The patient had no respiratory symptoms or signs of pulmonary involvement.

Discussion: LAM is predominantly a disease affecting the lungs in most cases. It typically presents with symptoms referral to diagnosis, including dyspnea on exertion, chest pain, cough, and pneumothoraces. In this case, the patient presented with vomiting, obstipation, rectal bleeding, and chest pain. The differential diagnosis included gastrointestinal or urological causes. The diagnosis of LAM should be considered in patients with gastrointestinal symptoms and a history of TSC.

Antiemetic therapy with metoclopramide and ondansetron was started, and the patient was referred to a pulmonologist for further evaluation. The pulmonologist confirmed the diagnosis of LAM and initiated treatment with sirolimus, a mTOR inhibitor. The patient experienced improvement in symptoms and a decrease in tumor size on follow-up imaging.

Conclusion: This case highlights the importance of considering LAM in patients with unexplained gastrointestinal symptoms and a history of TSC. Early diagnosis and treatment with mTOR inhibitors are crucial for improving outcomes in patients with this rare disease.
**Extraskelatal pulmonary osteosarcoma masquerading as tuberculosis**

Yoslay Perez, Rene Rico, David Ashkin and Andreas Schmid

**Introduction:** Extraskelatal 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 extraskelatal osteosarcoma of the lung referred to our institution for the management of pulmonary tuberculosi.

**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 afibrile, 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 extraskelatal osteosarcoma of the lung.

**Discussion:** Extraskelatal 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 47.5-62.0 years and a slight male predominance [4-9]. Most tumors occur in the lower extremities (48%), the upper extremities (23%), the retroperitoneal (17%), and the trunk (10-11%) [4-8, 9]. To our knowledge, only a handful of cases have been reported of intrathoracic extraskelatal 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 potential diagnoses such as this rare malignancy.

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**Perivascular epithelioid cell tumors in lymphangiomyomatosis: A new association**

Kaantha Medepalli and Marilyn Glasberg

**Introduction:** Renal angionyolipomas (AMLs) and perivascular epithelioid 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 PEComas associated with lymphangiomyomatosis (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 swelling.

**Case Report:** A 49 years old woman of Hispanic origin, with known past medical history of LAM and hypertension with obesotrophy 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 swelling, 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 diagnosis or within a year difference; rarely does it precede the latter. There are several hypotheses thought to play a role in the pathogenesis of cancer and sarcoiasis. Among those, ultraviolet light is thought active an inflammatory cascade contributing to both entities, however a definitive mechanism of pathogenesis is unknown.

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**Malignoma 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 and ophthalmologic systems. Sarcoidosis is often referred to as the great mimicker, given the 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 afibrile, 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, Coccidiomycosis, 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 hypotheses thought to play a role in the pathogenesis of cancer and sarcoidosis. Among those, ultraviolet light is thought active in inflammatory cascade contributing to both entities, however a definitive mechanism of pathogenesis is unknown.

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**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 developing 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.

**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 a 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 11 mm right upper lobe attenuation and 7 mm subpleural non-calcified nodule as well as 5 mm 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. 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.

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

Arnaldo Reyes, Nillian Zamot, Gustavo Ferrer, Hector Varquez-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.

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 24.6 mg/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 0.6 K/cmm, IgE levels of 396.8 IU/mL. However, Aspergillus IgG, precipitin and Anti-neutrophil 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. 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 neoplasms. 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: Intersitial lung disease (ILD) has been reported in NF1 with an incidence of 5.5 to 23%. 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. Although data is limited, in cases of NF1 with ILD documented with biopsy, histopathologic patterns reported include non-specific interstitial pneumonia (NSIP), chronic eosinophilic pneumonia. 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, anthelmintic 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 sputum 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.
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 the primary analysis population.

Results: Analysis included 3,589 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 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, Henrich 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 18μg. Assessments included: change from baseline in 1-h morning post-dose FEV1, co-primary endpoint: AB/FF vs AB; change from baseline in morning pre-dose FEV1, co-primary endpoint: AB/FF vs FF; AUC0–3/3h FEV1; 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 FEV1 was 50.3% predicted. At Week 24, patients receiving AB/FF had significantly improved 1-h post-dose FEV1, vs AB or FF, significantly improved trough FEV1, vs FF, and significantly improved AUC0–3/3h FEV1 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 improvements with AB/FF significantly improved 1-h post-dose bronchodilation vs AB and trough FEV1 vs FF.

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 FEV1 vs FF.

Funding: Circassia

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

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

Introduction: We used data from a Phase IIb 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 SpO2 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 IIb 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 enrollment 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

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

W. Gerald Teague, Leonard B. Bacharier, Timrah Haselkorn, Ahmar Iqbal, David R. Mink, Cynthia Alvarez, Bradley E. Chippas

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, and obesity. In adolescents with severe asthma, different factors were associated with lung function decline.

Funding: Genentech, Inc.

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. Chippas, Noelle M. Griffin, Benjamin L. Trzaska, 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 [5.6]). Similar improvements were seen in adult asthma patients. Moderate 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.

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

Jonathan Corren, Jane R. Pames, 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/NEO19929), 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. 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], 120 mg every 4 weeks [medium dose], 280 mg every 4 weeks [high dose]) or placebo in a Phase 2 study (NCT03054130). AQLQ(S)+12 was evaluated every 4 weeks (score range: 1–7; increase in value indicates improvement; minimal clinically important difference: 0.5) 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 78.8% (p=0.001) for low-, 76.3% (p=0.02) for medium- and 76.8% (p=0.04) for high-dose tezepelumab, vs 63.8% (p=0.03) for placebo. Overall, 74.8% (p=0.029) of patients receiving tezepelumab achieved improvements ≥5 points from baseline vs 63.8% (p=0.07) 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
Benralizumab improves morning peak inspiratory flow while reducing oral corticosteroid dosages for patients with severe, uncontrolled asthma in the ZONDA Phase III Trial

Nitin L. Lugogo, Joel N. Kîné, Ian Hirsch, Mitchell Goldman, James G. Zangrilli, Frank Trud

Introduction: Add-on oral corticosteroid (OCS) treatment is used to manage symptoms of patients who have uncontrolled asthma despite receiving high-dose inhaled corticosteroids plus long-acting β2-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 (NC1I 2I05/25525; Nair et al. N Eng 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).

We here evaluate the impact of benralizumab treatment and reduced OCS use on lung function, as assessed by peak expiratory flow (PEF), for patients in the ZONA trial.

Methods: The ZONA trial included patients (aged 18–75 years) with severe, uncontrolled asthma (eosinophil counts ≥ 150 cells/µL) who were receiving high-dose ICS/LABA and had OCS titrated to the minimum effective dosage (baseline) without losing asthma control. Patients received benralizumab 30 mg subcutaneously (SC) every 4 weeks (Q4W) or every 8 weeks (Q8W; first three doses Q4W, n = 496) or placebo (n = 496). FAO was defined as a ratio of postbronchodilator forced expiratory volume in one second (FEV1) 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 [1.1–64.0] 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]): 550 [300–4,484] 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 Q4W 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 FEV1, 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

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 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
Impact of body mass index on efficacy of benralizumab in patients with severe, uncontrolled eosinophilic asthma: pooled analysis of the SIROCCO and CALIMA Trials
Frank Trudo, Ian Hinch, Gokul Gopalan, Ubaldo Martinez

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-dose inhaled corticosteroids/long-acting β₂-agonists with baseline blood eosinophil ≥500 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 as normal/underweight (BMI <25 kg/m²), overweight (BMI 25–30 kg/m²), or obese (BMI ≥30 kg/m²). Efficacy outcomes included annual exacerbation rate and change from baseline to end of treatment in prebronchodilator forced expiratory volume in 1 second (FEV₁) 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., Q4W, rate ratio 0.53 (0.11–2.12), respectively), and numerical improvements were observed with benralizumab (both dosages) vs. with placebo for the obese group. Increases in prebronchodilator FEV₁ from baseline were greater with benralizumab treatment vs. with placebo for the normal/underweight and overweight groups (e.g., Q4W: 0.148 and 0.214 L, respectively, nominal p=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 FEV₁ improvements were numerically favored benralizumab. Improvements, particularly in FEV₁, were less robust for obese patients.

Funded by: AstraZeneca

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
Eric T. Wittbrodt, Lauren A. Millette, Gary T. Ferguson, Kristin Evans, Joseph Tkacz

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-index (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 pulmonaryologist 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.

Funded by: AstraZeneca

What symptomatic patients with asthma and chronic obstructive pulmonary disease (COPD) find important in their maintenance inhaler therapy: A focus group study
Ileen Gilbert, Natalia Hawken, Nicola A. Hanania, Fernando Martinez, Tommi Tervonen

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.

Conclusion: 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.

Funded by: AstraZeneca

The effect of season on hospitalization and mortality in patients with idiopathic pulmonary fibrosis treated with pirfenidone versus placebo
Brett Ley, Rishi Raj, Benjamin Tzaskoma, 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 (NCT00287929 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 was 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 (4.8% 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.
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.

Funding: Boehringer Ingelheim

Omalizumab: More than 15 years of health impact in asthma

Luisa Alvaraes, Madhusubramanian Muthukumar, Santanu Mukhopadhyay, Paraskevi A. Katsaounou

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
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%) vs 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% and 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, 3.5%; GLY 25 mcg, 1.1%; GLY 50 mcg, 2.2%; low: 0.7% vs 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, 23.1 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: 13.6 vs 6.7; TIO vs placebo, 13.6 vs 13.0). 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 (placebo vs GLY 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 CV and COPD risk factors for up to 48 weeks.

Funding: Sunovion

Lung function and patient-reported outcomes response to glycopyrrolate (SEEBR™ 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 Obar

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 (NCT01798864) 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 to 12 hours (FEV1, AUC0–12h), St. George’s Respiratory Questionnaire (SGRQ) total score, and Transition Dyspnea Index (TDI) focal score. FEV1 reversibility was calculated as percentage increase of FEV1, after inhalation of a bronchodilator, compared to FEV1, before bronchodilator inhalation. Reversibility was defined as a post-bronchodilator increase of ≥12% and ≥200 mL in FEV1.

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 FEV1, AUC0–12h 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 vs -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

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 (LABA+ICS [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 one second (FEV1; -3.888 vs placebo, p<0.001) in LABA subgroups at week 12. The overall change from baseline in trough FEV1 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<0.001), 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: 35.7%). Over 48 weeks, change from baseline SGRQ in the LABA+yes subgroup was -5.190 for GLY and -3.094 for TIO. Cardiovascular safety and efficacy of nebulized glycopyrrolate/eflow cs in phase 3 trials of patients with moderate to very severe COPD

Funding: Sunovion
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 (PAR1 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 (FEV1 % pred) and age.

Methods: In two 12-week studies (n=1294; 31% on background long-acting β2-agonist + inhaled corticosteroids), lung function, health status, exacerbations and safety were assessed in subgroups: FEV1 % pred <50% and ≥50%; and age <65, 65-75, 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=433, 432) produced significant (p<0.05) and clinically important improvements in trough FEV1 vs placebo in all subjects (56 and 61 mL; n=121, 127) and in FEV1 % pred <50% (79 and 79 mL; n=183, 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 (-5.346 and -2.714) vs placebo and in the FEV1 % pred <50% (-3.237 and -2.687) 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-severe COPD limited, including those aged ≥75 years.

Funding: Sunovion

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-Godyf, 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 (FEV1 AUC0–12h; 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 FEV1, AUC0–12h 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 (-3.9, 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 (FEV1, AUC0–12h; L), St. George’s Respiratory Questionnaire (SGRQ) total score, and Transition Dyspnea Index (TDI) score. Any history of asthma was an exclusionary criterion. FEV1 reversibility was calculated as percentage increase of FEV1 after sequential inhalation of short-acting (anticholinergic and beta2-agonist) bronchodilators. Reversibility was defined as a post-bronchodilator increase of ≥12% and ≥200 L in FEV1.

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 FEV1, AUC0–12h 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 (-6.1, 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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