RESPIROLOGY

CARE™ PERSPECTIVES

ATS 2016

Conference Report on Respirology

Commentary and content provided by the CARE Respirology Faculty

ATS 2016 - AMERICAN THORACIC SOCIETY - **SAN FRANCISCO, CA** - MAY 13-18

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CARE™ PERSPECTIVES

ATS 2016

Conference Report on Respirology

This issue of CARE Perspectives explores relevant abstracts and research presented at the ATS conference within the fields of cystic fibrosis, chronic obstructive pulmonary disease, non-CF bronchiectasis, asthma, pulmonary arterial hypertension, and biologics. Content is further contextualized and framed from a Canadian perspective.

We hope you find this valuable and we look forward to seeing you at ERS 2016!

Hartmut Grasemann, MD, PhD
Hospital for Sick Children, Toronto
Professor, University of Toronto

CONTENTS

The content that follows is written in the language in which it was presented. The following content is drawn from the abstracts at the ATS 2016 meeting, and is augmented with content and perspectives from the CARE Respirology Faculty.

CYSTIC FIBROSIS NEEDS ASSESSMENT

The CARE Respirology Faculty, led by Drs. Hartmut Grasemann and Felix Ratjen, have developed a needs assessment on cystic fibrosis. This needs assessment will seek to understand Canadian healthcare professionals' thoughts and current perspectives on the current treatment paradigm in Canadian practice.

This questionnaire can be found within this mailing or at: **www.CAREeducation.ca**

Please take 5 minutes to complete this questionnaire and share your thoughts. Your participation is greatly appreciated!

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CYSTIC FIBROSIS

ATS 2016. A2885 - Short-Term and Long-Term Effects of Ivacaftor Treatment on Sputum Microbiota in CF Patients with the G551D CFTR Mutation

L. Hoffman et al.

Results: Among the 8 culture-positive subjects, relative and absolute abundances of *P. aeruginosa* (by sequencing and qPCR, respectively) decreased significantly by days 7/8 compared with day 0, and both measures continued to decline between days 210 and 618, similar to culture results. No other significant, generalized and persistent changes in specific taxa were found, including for *Staphylococcus aureus*. However, total bacterial abundance also decreased significantly by day 7/8 and continued to decline between days 210-618, but at a lower overall rate than for *P. aeruginosa.* These changes resulted in trend towards increased overall diversity by days 7/8 that reached significance by day 415. Decreases in *P. aeruginosa* and in all bacteria correlated with improvement in the lung function measure FEV1 during the first week of treatment.

Conclusions: Ivacaftor treatment was followed by a rapid decrease in *P. aeruginosa* sputum abundance during the first week that was sustained for at least 618 days. There was a parallel decrease in abundance of all bacteria, but of lower magnitude, resulting in increased sputum microbial diversity at later time points. The decreases in both *P. aeruginosa* and in all bacteria correlated with spirometric improvement. While the reasons for the particularly strong effect on *P. aeruginosa* remain to be defined, these results suggest that addressing CFTR dysfunction improves overall bacterial clearance from sputum.

"**IVACAFTOR AND LUMICAFTOR** (ORKAMBI®) THERAPY HAS RECENTLY **BEEN APPROVED BY FDA AND HEALTH CANADA** FOR CF PATIENTS HOMOZYGOUS FOR THE MOST COMMON CFTR MUTATION"

ATS 2016. A5585 - Characterization of Ivacaftor and Lumacaftor Using BioMAP® Profiling - Implications for Cystic Fibrosis

S. Velichko et al.

Results: Using the DiscoveRx® PathHunter®Pharmacotrafficking assay specific for the delta-F508 mutation, we demonstrated that lumacaftor restored trafficking of CFTR to the cell surface, consistent with its mechanism of action. However, using our BioMAP Diversity PLUS phenotypic screening platform, we show that both ivacaftor and lumacaftor decrease several anti-inflammatory activities consistent with their clinical efficacy in CF. BioMAP systems are constructed using one or more human primary cell types pooled from healthy donors, and stimulated to recapitulate the complexity of disease biology. In a system modeling infection-mediated vascular inflammation, both ivacaftor and lumacaftor decreased prostaglandin E2 (PGE2) production, while IL-17 was decreased in a system modeling T cell activation and IL-8 production was decreased in a model of airway inflammation. Elevated IL-17 levels has been reported to be highly increased in the bronchoalveolar lavage (BAL) of CF patients; IL-17 drives IL-8 production, an important mediator of neutrophil recruitment, as well as PGE2 production, which mediates inflammatory responses via interaction with its various receptors.

Conclusions: This data suggests that the anti-inflammatory effects of compounds targeting CFTR in the BioMAP Diversity PLUS panel correlate with clinical outcomes. Although it remains to be determined whether these shared activities are due to direct effects on wild-type CFTR, this evidence points to an additional anti-inflammatory component of these agents that may be beneficial for the treatment of cystic fibrosis.

CARE FACULTY PERSPECTIVE: *Cystic fibrosis (CF) lung disease is characterized by chronic airway inflammation and infection. Whether CFTR-targeting drugs that lead to increased CFTR expression and function will also have effects on airway infection and/or inflammation in treated patients is an interesting question with clinical relevance. An antibacterial effect of Ivacaftor (Kalydeco®) treatment has repeatedly been observed. A study by Hoffman et al now illustrates that Ivacaftor resulted in decreased abundance of total bacteria and specifically P. aeruginosa in sputum of treated patients. P. aeruginosa is a CF pathogen that is often resistant to antibiotics and frequently results in chronic infections of CF airways. Velichko et al report in their study that both the CFTR potentiator Ivacaftor and the corrector Lumicaftor deploy anti-inflammatory effects in-vitro. Whether combination therapy of Ivacaftor and Lumicaftor will have anti-inflammatory or antibiotic effects in treated patients has yet to be demonstrated. Ivacaftor and Lumicaftor (Orkambi®) therapy has recently been approved by FDA and Health Canada for CF patients homozygous for the most common CFTR mutation (F508del/F508del).*

NON-CF BRONCHIECTASIS

ATS 2016. A2879 - Altered Lung Microbiota Profiles Are Associated with Disease Severity, Exacerbation Frequency and Neutrophilic Inflammation in Bronchiectasis

A. J. Dicker et al.

Results: The mean age of the patients was 64 years, 60% were female and 50% had idiopathic bronchiectasis. The microbiome of bronchiectasis patients was heterogeneous; some dominated by genera such as Haemophilus or Pseudomonas whilst other patients had a diverse microbiome with a combined predominance of Veillonella, Prevotella and Leptotrichia. A lower Shannon-Weiner Diversity Index was associated with multiple markers of disease severity including a higher BSI (P= 0.0003) and more frequent exacerbations (P= 0.008). Lower diversity or having a microbiota dominated with Haemophilus, Pseudomonas or Enterobacteriaceae sp. was significantly associated with higher levels of sputum myeloperoxidase and elastase (Figure) but not with Interleukin-1β or Interleukin-8.

Conclusions: A reduction in microbiome diversity or dominance of Pseudomonas is associated with airway inflammation and clinically relevant outcomes in bronchiectasis.

ATS 2016. A1775 - ORBIT-3 and ORBIT-4: Design of a Phase 3 Program to Investigate Safety and Efficacy of Pulmaquin® in Non-Cystic Fibrosis Bronchiectasis (NCFBE) Patients Chronically Colonized with Pseudomonas Aeruginosa (PA)

A. E. O'Donnell, MD et al.

Results: 1046 subjects were screened in the U.S., Canada, Australia, New Zealand, Israel, South Korea, Taiwan, South Africa, U.K., Germany, France, Spain, Italy, Ireland, Georgia, Serbia, Poland, Romania, Latvia and Peru. Both studies have completed enrollment with a total of 584 subjects randomized and dosed.

Conclusions: The two well-controlled clinical trials ORBIT-3 and -4 will provide a large database of well-defined NCFBE subjects with chronic PA colonization to investigate the effect of Pulmaquin on the prevention of PEs using a rigorous definition of exacerbation.

CARE FACULTY PERSPECTIVE: *Non-cystic fibrosis bronchiectasis (NCFBE) imposes a significant burden on affected individuals and the health care system. Prescribed treatment regimens for NCFBE infections and exacerbations are often not evidence-based. Clinical trials in well characterized populations are needed to optimize treatment in individuals with NCFBE. Outcomes of these trials will hopefully be presented soon.*

> "**CLINICAL TRIALS** IN WELL CHARACTERIZED POPULATIONS **ARE NEEDED TO OPTIMIZE TREATMENT IN INDIVIDUALS WITH NCFBE**. OUTCOMES OF THESE TRIALS WILL HOPEFULLY BE PRESENTED SOON."

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

ATS 2016. A6817 - Improvement in Lung Function and Symptom Control with Aclidinium Bromide Versus Tiotropium and Placebo in Symptomatic Patients with COPD: Post-Hoc Analysis of a Phase IIIb Study

J. Beier, et al.

Results: Overall, 277/414 symptomatic patients were included in the analyses (mean age 62.1 years; 65.0% male; 54.5% current smokers; baseline FEV_1 1.41±0.48 L). Aclidinium 400 µg BID improved FEV_1 over 24 hours from baseline at Week 6 compared with placebo. Additionally, improvements in FEV_1 from baseline during the nighttime period were observed for aclidinium 400 µg BID versus tiotropium. Aclidinium 400 µg BID demonstrated improvements in trough FEV_1 from baseline versus tiotropium and placebo at Week 6. Over the 6-week treatment period, aclidinium 400 µg BID improved early-morning and nighttime symptom severity, limitation of early-morning activities caused by COPD symptoms, and also improved E-RS total score and domain scores (at Week 6) versus tiotropium (except for E-RS Chest symptoms) and placebo. Tolerability (reported previously; Beier et al. 2013) showed similar incidence of adverse events (AEs) in each arm, with few anticholinergic AEs or serious AEs; aclidinium was well tolerated.

> "ACLIDINIUM BROMIDE IS **AVAILABLE IN CANADA AS SINGLE DRUG** OR IN COMBINATION WITH FORMOTEROL FUMARATE (LABA-LAMA)."

Spirometric and symptomatic variables in symptomatic patients with COPD (baseline E-RS ≥ 10)

	Day 1			Week 6		
Change from baseline in normalized FEV_1 vs placebo, mL	Aclidinium 400 µg	Tiotropium 18 µg	Aclidinium vs tiotropium	Aclidinium 400 µg	Tiotropium 18 µg	Aclidinium vs tiotropium
FEV_1 $AUC0_{0\text{-}24/24h}$	150*	87*	63ǂ	140**	106*	34
FEV_1 $AUC_{12\text{-}24/12h}$	157**	67*	90ǂ	153**	90**	63ǂ
FEV_1 $AUC_{0\text{-}12}$	147**	112**	35	126*	123*	3
Morning pre-dose (trough) FEV_1	136**	68*	68ǂ	137*	70*	65ǂ
E-RS Total Score over 6 weeks	-	-	-	-2.15*	-0.98	-1.17ǂ
[a]Early-morning symptom severity over 6 weeks (% reduction)	-	-	-	-0.25* (-9.54%)	-0.11 (-4.33%)	-0.14ǂ (-5.21%)
[a]Nighttime symptom severity over 6 weeks (% reduction)	-	-	-	-0.23* (-10.31%)	-0.09 (-4.23)	-0.14ǂ (-6.09%)
[b]Limitation of early-morning activity over 6 weeks (% reduction)	-	-	-	-0.21* (-9.09%)	-0.07 (-3.10%)	-0.14ǂ (-5.99%)

*p<0.05 vs placebo; **p≤0.0001 vs placebo; ǂ p<0.05 vs tiotropium
[a]Least squares mean change from baseline in the severity of symptoms over 6 weeks: 1= No symptoms, 2=Mild, 3=Moderate, 4=Severe, 5=Very severe
[b]Limitation of activity: 1=Not at all, 2= A little, 3=Moderately, 4= A good deal, 5=A very good deal
AUC, area under the curve; COPD, chronic obstructive pulmonary disease; E-RS, EXAcerbations of Chronic pulmonary disease Tool-Respiratory Symptoms; FEV_1, forced expiratory volume in 1 second

Conclusions: In symptomatic patients with moderate to severe COPD, aclidinium 400 µg BID improved bronchodilation (particularly during the nighttime period), and also improved early-morning, daytime, and nighttime symptoms, and early-morning limitation of activity compared with either tiotropium 18 µg QD or placebo.

CARE FACULTY PERSPECTIVE: *A number of clinical trials indicated that the long-acting, inhaled muscarinic antagonist (LAMA) aclidinium bromide reduces the frequency of COPD exacerbations compared with placebo and that these effects are greater in symptomatic patients. Aclidinium therefore offers an alternative to long-acting beta-agonist or anticholinergic bronchodilators. Aclidinium bromide is available in Canada as single drug or in combination with formoterol fumarate (LABA-LAMA).*

ATS 2016. A6816 - Treatment Satisfaction and Preference with Indacaterol/Glycopyrronium Fixed-Dose Combination Therapy in Comparison to Tiotropium Monotherapy - Results of the FAVOR Study

P. Kardos et al.

Results: 87 out of 88 randomized patients completed the study and showed significantly higher FEV1 1 h post-inhalation after 4 weeks treatment with IND/GLY compared to TIO (see table). Notably, patients that preferred IND/GLY (67%) showed a significant and clinically important increase in FEV1 1 h post-inhalation with IND/GLY compared to TIO (LSM difference, 109 ml; p<0.0001) whereas in patients that preferred TIO (29.5%), the FEV1 1 h post-inhalation was comparable between both treatments (LSM difference, -19 ml; p=0.8127). Importantly, a higher proportion of patients stated they were very satisfied or satisfied with IND/GLY treatment (79.3%) compared to TIO treatment (58.0%) with regard to dyspnea reduction after 4 weeks. The difference was even higher when considering shortness of breath on exertion (IND/GLY, 72.4% vs. TIO, 43.2%). In line with this, the TSQM-9 domain scores were significantly higher under IND/GLY compared to TIO for treatment effectiveness (score difference 12.6, p=0.0001) and global satisfaction (score difference 10.6, p=0.0035).

Conclusions: This study indicated that beyond FEV1, important patients reported outcomes improved with the dual bronchodilator IND/GLY compared to TIO monotherapy. Additional studies are now required to investigate how this treatment satisfaction/preference translates into improved adherence, activity and long term treatment outcomes.

CARE FACULTY PERSPECTIVE: *Guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with COPD and a high risk of exacerbations. Results of the FLAME study, recently published in the New England Journal of Medicine (Wedzicha et al., NEJM May 15, 2016), show that combination treatment with a once-daily inhaled formulation of indacaterol-glycopyrronium (LABA-LAMA) was more effective than LABA plus inhaled steroid (ICS) combination of salmeterol and fluticasone (Advair), in COPD patients with a history of exacerbations.*

> "GUIDELINES RECOMMEND EITHER A **LABA PLUS AN INHALED GLUCOCORTICOID OR A LAMA AS THE FIRST-CHOICE TREATMENT FOR PATIENTS WITH COPD** AND A HIGH RISK OF EXACERBATIONS."

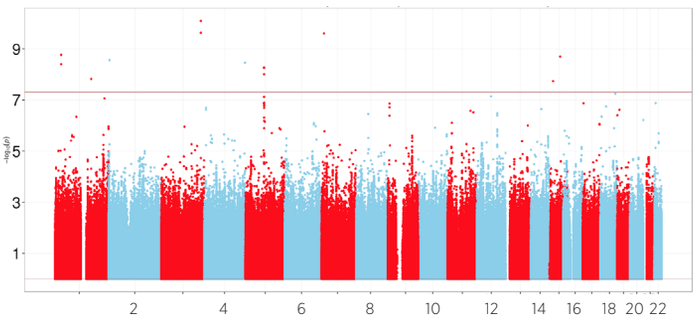
The annual rate of all COPD exacerbation was 11% lower in patients receiving LABA-LAMA than in those treated with LABA-ICS. Patients on LABA-LAMA had a longer time to the first exacerbation (71 vs 51 days). There was a 17% reduction in the rate of all exacerbations in the LABA-LAMA treated patients, compared with LABA-ICS, as well as a 19% reduction in hospital admissions for severe exacerbation. The once-daily LABA-LAMA combination regimen used in the FLAME study is approved in Canada and Europe (UltibroTM Breezhaler®).

ATS 2016. A4074 - Age, Sex and Genetic Factors Are Associated with Response to Ipratropium Among Individuals with Mild COPD in the Lung Health Study

M. Obeidat et al.

Results: In the 1,961 individuals receiving ipratropium, for every 10 years increase in age, FEV1 response to ipratropium decreased by 1.3 % (P= 3x10-4), and female sex was associated with a 3.6% increase in FEV1 response to ipratropium (P= 7 x10-8). GWAS of the quantitative change in FEV1 after 4 months of treatment revealed a number of loci reaching nominal significance with P values ranging from 1x10-5 to 1x10-7, and one locus on chromosome 3 yielding genome-wide significance (P<5x10-8). The genomic inflation factor was 1.01, indicating little or no bias due to population stratification. The Manhattan plot is shown below.

Manhattan Plot for FEV1-slope GWAS, all SNPs MAF > 1% R^2 > 0.5



Conclusions: Younger age and female sex were associated with greater improvements in FEV1 after ipratropium therapy. There are genetic variants associated with the quantitative measure change in FEV1 in response to the drug. This information could help identify individuals who are more likely to benefit from cholinergic antagonists.

ASTHMA

ATS 2016. A4332 - Dipeptidyl Peptidase-4 (DPP-4) Is a Novel Predictive Biomarker for the Investigational Anti-IL-13 Targeted Therapy Tralokinumab

K. Ranade et al.

Results:

Primary and key secondary efficacy endpoints for tralokinumab 300 mg eow in ITT and subgroups as assessed by a newly developed immunoassay for serum DPP-4

	ITT (N=150)[b]	DPP ≥ median (N=73)[b]	DPP ≥ median &no chronic OCS (N=67)[b]	DPP ≥ median & FEV1reversibility ≥12% and no chronic OCS (N=24)[b]
Primary endpoint				
Asthma exacerbation rate reduction[a]% (95% CI)	6 (–31, 33) *p*=0.709	42 (3, 66) *p*=0.038	46 (6, 69) *p*=0.03	71 (–3, 92) *p*=0.055
Secondary endpoints (difference from placebo)				
Percent change from baseline in FEV_1 (95% CI)	7.28 (2.55,12.02) p=0.003	10.92 (3.78,18.06) p=0.003	11.2 (3.79, 18.60) *p*=0.003	17.07 (–1.90, 36.04) *p*=0.077
Change from baseline in ACQ-6 (95% CI)	–0.19 (–0.43, 0.06) *p*=0.131	–0.49 (–0.84, –0.14) *p*=0.006	–0.54 (–0.92,–0.18) *p*=0.004	–1.33 (–2.04, –0.63) *p*<0.001
Change from baseline in AQLQ (95% CI)	0.21 (–0.05, 0.46) *p*=0.110	0.61 (0.22, 0.99) *p*=0.002	0.68 (0.27, 1.08) *p*=0.001	1.32 (0.47, 2.16) *p*=0.003

[a]Asthma exacerbation rate reductions were calculated using Poisson regression model adjusted for over dispersion with treatment group, age, gender, number of asthma exacerbations in the past year, atopic asthma status, presence or absence of chronic OCS use and geographic region as covariates and the log of number of days in the study as offset.
[b]Number of patients in 300-mg every-other-week group.
CI, confidence interval; FEV1, forced expiratory volume in 1 second; ITT, intention to treat; ACQ-6, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; OCS, oral corticosteroids.

Conclusions: These results provide new insight into IL-13 biology that is distinct from eosinophils and identify serum DPP-4 as a novel predictive biomarker for tralokinumab, which is in Phase III trials for severe asthma.

ATS 2016. A4351 - High Blood Eosinophil Concentrations and Serum Biomarkers of Low IL-13 Pathway Activation at Baseline Predict Exacerbation Rate Reduction by Benralizumab for Patients with Moderate to Severe Asthma

P. Newbold et al.

Results: Median baseline serum DPP-4 and periostin concentrations were 363.5 ng/mL (103.3–867.5) and 23.6 ng/mL (7.5–104.1), respectively. No linear correlations were observed between serum DPP-4 and blood eosinophils (correlation coefficient 0.05, *p*=0.22) or serum periostin (correlation coefficient 0.03, *p*=0.48). Serum periostin was linearly correlated with blood eosinophils (correlation coefficient 0.33,*p*<0.001). Eosinophil high, DPP-4 low, and periostin low statistically significantly predicted ERR with benralizumab. For the eosinophil high subgroup, ERR was independent of periostin. For the eosinophil low subgroup, periostin low yielded numerically greater ERR than periostin high. DPP-4 low was predictive of ERR for eosinophil high and identified numerically greater ERR for the eosinophil low subgroup.

Conclusions: High baseline blood eosinophil concentrations predicted benralizumab efficacy, and, effects were independent of periostin in this subgroup. Below-median baseline DPP-4 concentrations indicative of low IL-13 pathway activation predicted benralizumab efficacy and may identify patients with low blood eosinophil concentrations responsive to benralizumab. The biomarker of IL-13 pathway activation, DPP-4, may identify patient subsets who benefit from anti–IL-5R/eosinophil-depleting benralizumab (DPP-4 low) and IL-13–targeting tralokinumab (DPP-4 high).

CARE FACULTY PERSPECTIVE: *Moderate-to-severe asthma can be refractory to routinely prescribed medications such as inhaled corticosteroids, long-acting β-agonists, and leukotriene receptor antagonists. In these cases, individualized therapy may be needed. Biomarkers have been shown to be helpful in defining specific subtypes of asthma, identifying potential therapeutic targets, and may also help monitor the response to new therapies.*

PULMONARY ARTERIAL HYPERTENSION

ATS 2016. A6468 - A Randomized Open Label Study Comparing First-Line Treatment with Bosentan or Sildenafil in Chronic Thromboembolic Pulmonary Hypertension

E. Gotti, et al.

Results: 121 CTEPH patients were randomized: 61 to the B group [median age: 70 (53÷74) years, Female/Male: 41/20] and 60 to the S group [median age: 68 (49÷75) years; Female/Male: 27/33]. Four patients (6.5 %) in the B group and 4 (6.6%) in the S group did not complete the short term evaluation because of death, pulmonary endoarterectomy before re-evaluation or adverse events. 57 patients in the B group and 56 in the S group completed the study (mean treatment period: 4.2 ± 2.7 months).

Patient outcomes with first-line treatment of Bosentan or Sildenafil

	6MWT (m)	RAP (mmHg)	mPAP (mmHg)	CI (l/min/m²)	PVR (WU)	MVO2 (%)
Baseline	411 (246÷484)	8 (5÷11)	45 (37÷52)	2.4 (2.1÷3.0)	8.0 (5.9÷11.6)	63 (60÷69)
B	422 (273÷500)	7 (5÷10)	40 (34÷47)	2.7 (2.4÷3.1)	6.1 (4.2÷8.8)	66 (62÷71)
p-value	0.01	0.4	<0.001	<0.001	<0.001	0.038
Baseline	403 (322÷491)	7 (5÷10)	47 (42÷54)	2.6 (2.2÷2.8)	7.7 (6.7÷9.8)	64 (59÷69)
S	447 (363÷525)	6 (4÷8)	42 (37÷46)	2.8 (2.5÷3.2)	6.2 (4.8÷7.7)	67 (62÷72)
p-value	<0.001	0.001	<0.001	<0.001	<0.001	0.001
p changes B vs changes S	0.01	0.122	0.378	0.360	0.782	0.346

Legend: CI: cardiac index; MVO2: mixed venous oxygen; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; WU: Wood unit.

Conclusions: Both bosentan and sildenafil therapy is associated with improvements in exercise capacity and hemodynamics in operable and not operable CTEPH; no differences were observed among the two drugs except for the increase in exercise capacity in favor of sildenafil.

ATS 2016. A6315 - The RESPITE Study: Riociguat in Patients with PAH and an Inadequate Response to Phosphodiesterase 5 Inhibitors

M. M. Hoeper et al.

Results: Thirty patients (mean±SD age 57±12 years; 73% female) were eligible for this interim analysis; 26 (87%) completed the study. Patients were pretreated with sildenafil (n=21) or tadalafil (n=9); 22 (73%) also received an ERA. At baseline, all patients were in FC III; by Week 24, 50% had improved to FC II. From baseline to Week 24, mean±SD 6MWD increased from 353±78 m to 392±112 m (n=25); mean±SD pulmonary vascular resistance decreased from 856±266 dyn•sec•cm-^{5} to 772±465 dyn•sec•cm-^{5} (n=25); mean±SD cardiac index increased from 2.2±0.3 L/min/m^{2} to 2.6±0.6 L/min/m^{2} (n=25); and mean±SD NT-proBNP levels decreased from 2208±2961 pg/mL to 817±1066 pg/mL (n=26). Four patients (13%) experienced clinical worsening events, including 3 deaths: one patient died from subdural hematoma after a fall and one patient died from pneumonia, neither of which were considered study drug-related; the other patient died from an unknown cause during the extension period of the study. The most frequent study drug-related adverse events were headache (17%), dyspepsia (13%), epistaxis (13%), and dizziness (10%).

Conclusions: In this interim analysis of RESPITE, riociguat improved 6MWD, hemodynamics, NT-proBNP levels, and WHO FC in PAH patients previously treated with PDE5i. No new safety signals were observed. These preliminary data support the hypothesis that patients with PAH who have an insufficient response to PDE5i therapy may benefit from a transition to riociguat. Randomized controlled trials are required to further investigate this approach.

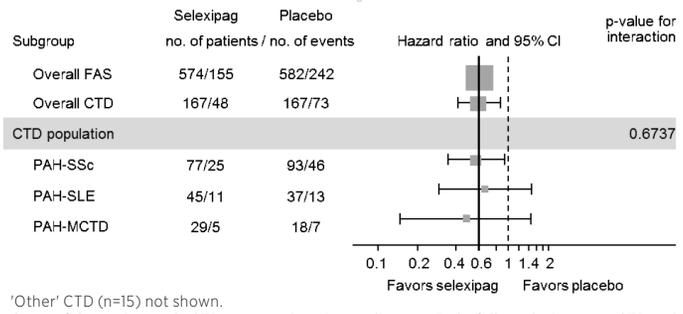
CARE FACULTY PERSPECTIVE: *Riociguat is a stimulator of soluble guanylate cyclase, the receptor for nitric oxide (NO), and is approved in Canada for the management of inoperable chronic thromboembolic pulmonary hypertension (CTEPH). The RESPITE study is an open-label, international, multicenter, single-arm, uncontrolled, phase IIIb study of riociguat in patients with pulmonary arterial hypertension (PAH) with insufficient response to treatment with Phosphodiesterase-5 inhibitors (PDE-5i). The interim analysis of RESPITE that was presented at ATS suggests efficacy of riociguat in these patients with PAH.*

ATS 2016. A6466 - Targeting the Prostacyclin Pathway in the Treatment of Connective Tissue Disease Associated Pulmonary Arterial Hypertension (PAH): Insights from the Randomized Controlled GRIPHON Trial with Selexipag

S. P. Gaine et al.

Results: Of the 334 PAH-CTD enrolled, 170, 82, 47 had PAH-SSc, PAH-SLE and PAH-MCTD, respectively. In 35 patients, the CTD sub-classification was not reported, and therefore data from these patients are not included. In the 3 PAH-CTD subgroups, the majority of patients were female (84–99%) and were receiving an endothelin receptor antagonist, a phosphodiesterase type-5 inhibitor or both at baseline (73–83%). In the PAH-SSc, PAH-SLE and PAH-MCTD groups, the mean (SD) age was 60.0 (10.6), 39.0 (11.3) and 48 (14.7) years, respectively, and 65%, 33% and 45% were in WHO functional class III, respectively. Selexipag reduced the risk of morbidity/mortality events by 44% (0.56; 0.34–0.91) in PAH-SSc, by 34% (0.66; 0.30–1.48) in PAH-SLE, and by 53% (0.47; 0.15–1.48) in PAH-MCTD patients (Figure). The treatment effect was consistent across the PAH-CTD subgroups (interaction test indicated no heterogeneity; p=0.6737). By the end of study, 22 PAH-SSc, 7 PAH-SLE and 3 PAH-MCTD patients in the placebo and 17 PAH-SSc, 4 PAH-SLE, 8 PAH-MCTD patients in the selexipag group had died. Common prostacyclin-associated side effects observed with selexipag in PAH-CTD patients (e.g. headache, diarrhea, nausea) generally occurred at a similar incidence to PAH-non-CTD patients and within the PAH-CTD subgroups.

Subgroup analysis of Selexipag vs. Placebo



'Other' CTD (n=15) not shown.
CI, confidence interval; CTD, connective tissue disease; FAS, full analysis set; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; SLE, systemic lupus erythematosus; SSc, systemic sclerosis

Conclusions: The GRIPHON study included the largest randomized cohort of PAH-CTD patients to date. The treatment effect of selexipag on the time to first morbidity/mortality event was consistent across the PAH-SSc, PAH-SLE and PAH-MCTD sub-groups. These data suggest that targeting the prostacyclin pathway with selexipag is an effective therapeutic option in these difficult-to-treat patients.

CARE FACULTY PERSPECTIVE: *Selexipag is a first-in-class, orally available, selective IP prostacyclin-receptor agonist, that may add to the rapidly growing therapeutic advancements seen in PAH management. The GRIPHON trial, a phase III study of selexipag, demonstrated that among patients with PAH, the risk of the primary composite end point of death or a complication related to PAH was significantly lower with selexipag than with placebo. Results of the GRIPHON trial were recently published in the New England Journal of Medicine (Sitbon et al., NEJM 2015 ;373:2522-33).*

> "SELEXIPAG IS A **FIRST-IN-CLASS, ORALLY AVAILABLE**, SELECTIVE IP PROSTACYCLIN-RECEPTOR AGONIST, THAT MAY ADD TO THE **RAPIDLY GROWING THERAPEUTIC ADVANCEMENTS** SEEN IN PAH MANAGEMENT."

BIOLOGICS AND PNEUMONIA RISK

ATS 2016. A1592. Infectious Complications in Patients Receiving Biologic Therapy

C. Ochoa et al.

Results: A total of 97 patients with IBD and rheumatologic disorders initiated on anti-TNF alpha therapy were identified. The median age was 53 and 86% of the cohort was male. The most common comorbid conditions included diabetes, hypertension, and respiratory disease. The majority of patients received biologic therapy for greater than 24 months, 45% of patients had an infection leading to antibiotic administration during biologic therapy. 19% of these infections (18 events) resulted in hospitalization (serious infections). Of note, only 4 serious infections were seen with rheumatologic disorders while 14 serious infections occurred within the IBD population ($p<0.06$). The rate of serious infection for patients with IBD was 6.5 per 100 patient years of therapy. 89% of the cohort received steroid therapy at some point during or prior to biologic therapy. The most common infection demonstrated was respiratory (18 unique events) followed by genitourinary and soft tissue.

Conclusions: These results suggest that infections are increased in patients receiving anti-TNF alpha therapy for IBD and rheumatologic conditions. The overall rate of infection (serious plus uncomplicated) was not significantly different between the two cohorts. However, patients with IBD suffered from a higher frequency of serious infections compared to those with rheumatologic conditions. Respiratory infections occurred most frequently in both groups and concurrent use of steroids increased the propensity for infection.

CARE FACULTY PERSPECTIVE: *Biologics are increasingly used in patients with rheumatologic conditions and inflammatory bowel disease (IBD). This retrospective single center study included 97 patients with biopsy-proven IBD and rheumatologic conditions that were treated with anti-tumor necrosis factor-alpha (TNFα) drugs adalimumab, etanercept, or infliximab. In addition to their rheumatologic diagnoses or IBD, 40% were diagnosed with hypertension, 27% had diabetes, and 7% were diagnosed with COPD. 45% of patients had an infection leading to administration for antibiotic treatment during biologic therapy. 19% of these infections (18 events) resulted in hospitalization. The most common infection demonstrated was respiratory. Thus, the risk for infections in patients on biologics is increased and the concurrent use of steroids in these patients may contribute to the infection risk.*

> "**THE RISK FOR INFECTIONS IN PATIENTS ON BIOLOGICS IS INCREASED** AND THE CONCURRENT **USE OF STEROIDS** IN THESE PATIENTS **MAY CONTRIBUTE TO THE INFECTION RISK**."

ABOUT THE CARE RESPIROLOGY FACULTY

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