REVIEW

http://dx.doi.org/10.4046/trd.2014.77.4.155
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2014;77:155-160

TRD
Tuberculosis and Respiratory Diseases

Chronic Obstructive Pulmonary Disease: Respiratory Review of 2014

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Chronic obstructive pulmonary disease (COPD) is characterized by a diverse array of pulmonary and nonpulmonary manifestations, but our understanding of COPD pathogenesis and the factors that influence its heterogeneity in disease presentation is poor. Despite this heterogeneity, treatment algorithms are primarily driven by a single measurement, forced expiratory volume in 1 second (FEV_1) as a percentage of its predicted value (FEV_1%). In 2011, a major shift in Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment recommendations was proposed that stratifies patients with COPD on the basis of symptoms and exacerbation history. This article reviews the work reported in 2013 that enlightens our understanding of COPD with respect to COPD classification systems, phenotype, biomarker, exacerbation, and management for patients with COPD.

Keywords: Pulmonary Disease, Chronic Obstructive; Pulmonary Disease, Chronic Obstructive; Review

Introduction

Chronic obstructive pulmonary disease (COPD) represents a spectrum of lung diseases characterised by persistent airflow limitation due to varing combinations of small-airways disease and emphysema. It is a major cause of morbidity and disability, having a prevalence of around 10% in those aged over 40 years. By 2030 COPD is predicted to have become the third-leading cause of death worldwide. This review 6 articles focuses on COPD update published in major medical journals in 2013.

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Received: Jun. 22, 2014
Revised: Jun. 27, 2014
Accepted: Jul. 4, 2014

COPD Classification Systems

Characteristics, stability and outcomes of the 2011 GOLD COPD groups in the ECLIPSE cohort. Agusti et al.[1] Eur Respir J 2013;42:636-46.

The 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifies patients with chronic obstructive pulmonary disease (COPD) into four groups (A to D). We explored the characteristics, stability and relationship to outcomes of these groups within the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) (n = 2101). Main results showed that: 1) these groups differed in several clinical, functional, imaging and biological characteristics in addition to those used for their own definition; 2) A and D groups were relatively stable over time, whereas groups B and C showed more temporal variability; 3) the risk of exacerbation over 3 years increased progressively from A to D, whereas that of hospitalisation and mortality were lowest in A, highest in D and intermediate and similar in B and C, despite the former having milder airflow limitation. The prevalence of comorbidities and persistent systemic inflammation were highest in group B. The different longitudinal behaviour of group A versus B and C versus D (each pair with similar forced expiratory volume in1 s (FEV1) values supports the 2011 GOLD proposal of assessing COPD patients by more than FEV1 only. However the assumption that symptoms do not equate to risk appears to be naïve,

as groups B and C carry equally poor clinical outcomes, though for different reasons. *(Agusti et al.[1]; Reproduced with permission of the European Respiratory Society ⓒ. Eur Respir J September 2013,42:636-646; doi:10.1183/09031936.00195212.)*

1. Comments

This is the first study to show the temporal stability of the four 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups compared with 2007 GOLD groups in terms of patients distribution and disease severity using ECLIPSE cohort for 3 years. Recently, some studies have examined existing COPD cohorts in different aspects of new 2011 GOLD Classification[2,3]. This study shows that the 2011 GOLD classification had a high concordance rate for predicting exacerbations and hospitalizations compared with the 2007 GOLD classification. For follow-up periods, A and D groups did remain in their original groups, but B and C groups showed higher temporal variability. These findings suggest either disease progression or therapeutic effect. And these variability raise the concern the evidence of heterogeneity in natural history of COPD. It is not clear about untreated or mild COPD patients because this study was based on hospitalized patients.

Biomarker

The association of adiponectin with computed tomography phenotypes in chronic obstructive pulmonary disease. Carolan et al.[4] Am J Respir Care Med 2013;188: 561-6.

RATIONALE: Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder associated with systemic manifestations that contribute to its morbidity and mortality. Recent work suggests that biomarker signatures in the blood may be useful in evaluating COPD phenotypes and may provide insight into the pathophysiology of systemic manifestations. Adiponectin, primarily produced by fat cells, has been implicated in the pathophysiology of emphysema.
OBJECTIVES: To investigate the association of adiponectin with clinical and radiologic COPD phenotypes.
METHODS: Adiponectin levels were determined in 633 individuals, including 432 individuals with COPD from a cohort of former or current smokers enrolled in the COPDGene study. Univariate and multiple regression analysis were used to examine the association of adiponectin with clinical and physiologic data together with quantitative high-resolution computed tomography parameters.
MEASUREMENTS AND MAIN RESULTS: Multiple regression analysis confirmed that higher plasma adiponectin levels were independently associated with emphysema, decreasing body mass index, female sex, older age, and lower percentage change in prebronchodilator/post-bronchodilator FEV1.
CONCLUSIONS: The association between plasma adiponectin and computed tomography-assessed emphysema suggests a contribution of adiponectin to the development of emphysema and highlights a role for metabolic derangements in the pathophysiology of emphysema. *(Carlolan et al.[4], 2013, p. 561; Reprinted with permission of the American Thoracic Society. Copyright ⓒ 2014 American Thoracic Society. Official Journal of the American Thoracic Society.)*

1. Comments

It is well known that blood biomarkers are associated with the phenotypes of COPD and adiponectin is one of them[5]. The expression of adiponectin was increased in bronchoalveolar lavage fluid and airway epithelial of emphysema and COPD patients and some report suggest that it was important in the pathogenesis of smoking-related lung disease[6].

For the first time, this study demonstrates that adiponectin levels are associated with computed tomography-assessed emphysema. A limitation of this study was that the majority of study population was non-Hispanic white so it is not clear in other populations.

Exacerbations

Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. Molyneaux et al.[7] Am J Respir Crit Care Med 2013;188:1224-31.

RATIONALE: Rhinovirus infection is followed by significantly increased frequencies of positive, potentially pathogenic sputum cultures in chronic obstructive pulmonary disease (COPD). However, it remains unclear whether these represent de novo infections or an increased load of organisms from the complex microbial communities (microbiome) in the lower airways.
OBJECTIVES: To investigate the effect of rhinovirus infection on the airway bacterial microbiome.
METHODS: Subjects with COPD (n = 14) and healthy control subjects with normal lung function (n = 17) were infected with rhinovirus. Induced sputum was collected at baseline before rhinovirus inoculation and again on Days 5, 15, and 42 after rhinovirus infection and DNA was extracted. The V3-V5 region of the bacterial 16S ribosomal RNA gene was amplified and pyrosequenced, resulting in 370,849 high-quality reads from 112 of the possible 124 time points.
MEASUREMENTS AND MAIN RESULTS: At 15 days after rhinovirus infection, there was a sixfold increase in 16S copy number (P = 0.007) and a 16% rise in numbers of proteobacterial sequences, most notably in potentially pathogenic Haemophilus

influenzae (P = 2.7 × 10(-20)), from a preexisting community. These changes occurred only in the sputum microbiome of subjects with COPD and were still evident 42 days after infection. This was in contrast to the temporal stability demonstrated in the microbiome of healthy smokers and nonsmokers.
CONCLUSIONS: After rhinovirus infection, there is a rise in bacterial burden and a significant outgrowth of Haemophilus influenzae from the existing microbiota of subjects with COPD. This is not observed in healthy individuals. Our findings suggest that rhinovirus infection in COPD alters the respiratory microbiome and may precipitate secondary bacterial infections. *(Molyneaux et al.[7], 2013, p.1224, Reprinted with permission of American Thoracic Society. Copyright ⓒ 2014 American Thoracic Society. Official Journal of the American Thoracic Society.)*

1. Comments

Exacerbations of COPD are frequently caused by viral or bacterial infection. Culture independent techniques investigating respiratory sample demonstrated the composition of the lower respiratory tract microbiome in COPD[8]. The authors have shown that experimental rhinovirus infection induces the clinical feature of COPD exacerbations previously[9]. Secondary bacterial infection is common after rhinovirus infection in COPD and is associated with high levels of neutrophil elastase[10]. This study is the first controlled experiment to evaluate the effect of rhinovirus infection on the airway microbiome and it shows how the study patients have a significant change in burden and community of bacteria in lower airways as a response to rhinovirus infection. We need more studies to demonstrate the clinical pertinence of these results. If these finding are proven, effective prevention and management of viral infection such as enhancing innate immunity in COPD could reduce secondary bacterial infections and use of antibiotics in virus-induced COPD exacerbations. One potential limitation is that this study subjects are mild COPD patients with a forced expiratory volume in 1 second (FEV_1) greater than 50% predicted.

Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. Leuppi et al.[11] JAMA 2013;309:2223-31.

IMPORTANCE: International guidelines advocate a 7- to 14-day course of systemic glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease (COPD). However, the optimal dose and duration are unknown.
OBJECTIVE: To investigate whether a short-term (5 days) systemic glucocorticoid treatment in patients with COPD exacerbation is noninferior to conventional (14 days) treatment in clinical outcome and whether it decreases the exposure to steroids.
DESIGN, SETTING, AND PATIENTS REDUCE: (Reduction in the Use of Corticosteroids in Exacerbated COPD), a randomized, noninferiority multicenter trial in 5 Swiss teaching hospitals, enrolling 314 patients presenting to the emergency department with acute COPD exacerbation, past or present smokers (≥20 pack-years) without a history of asthma, from March 2006 through February 2011.
INTERVENTIONS: Treatment with 40 mg of prednisone daily for either 5 or 14 days in a placebo-controlled, double-blind fashion. The predefined noninferiority criterion was an absolute increase in exacerbations of at most 15%, translating to a critical hazard ratio of 1.515 for a reference event rate of 50%.
MAIN OUTCOME AND MEASURE: Time to next exacerbation within 180 days.
RESULTS: Of 314 randomized patients, 289 (92%) of whom were admitted to the hospital, 311 were included in the intention-to-treat analysis and 296 in the per-protocol analysis. Hazard ratios for the short-term vs conventional treatment group were 0.95 (90% CI, 0.70 to 1.29; P = .006 for noninferiority) in the intention-to-treat analysis and 0.93 (90% CI, 0.68 to 1.26; P = .005 for noninferiority) in the per-protocol analysis, meeting our noninferiority criterion. In the short-term group, 56 patients (35.9%) reached the primary end point; 57 (36.8%) in the conventional group. Estimates of reexacerbation rates within 180 days were 37.2% (95% CI, 29.5% to 44.9%) in the short-term; 38.4% (95% CI, 30.6% to 46.3%) in the conventional, with a difference of -1.2% (95% CI, -12.2% to 9.8%) between the short-term and the conventional. Among patients with a reexacerbation, the median time to event was 43.5 days (interquartile range [IQR], 13 to 118) in the short-term and 29 days (IQR, 16 to 85) in the conventional. There was no difference between groups in time to death, the combined end point of exacerbation, death, or both and recovery of lung function. In the conventional group, mean cumulative prednisone dose was significantly higher (793 mg [95% CI, 710 to 876 mg] vs 379 mg [95% CI, 311 to 446 mg], P < .001), but treatment-associated adverse reactions, including hyperglycemia and hypertension, did not occur more frequently.
CONCLUSIONS AND RELEVANCE: In patients presenting to the emergency department with acute exacerbations of COPD, 5-day treatment with systemic glucocorticoids was noninferior to 14-day treatment with regard to reexacerbation within 6 months of follow-up but significantly reduced glucocorticoid exposure. These findings support the use of a 5-day glucocorticoid treatment in acute exacerbations of COPD. *(Leuppi et al.[11], 2013, p. 2223; Reprinted with permission of American Medical Association)*

1. Comments

Current guidelines recommend that acute exacerbations of COPD be treated with systemic corticosteroid for 7 to 14

days but the optimal strategy for dosing and administration of these medications continues to be debated[12,13]. Systemic steroid therapy results in moderate improvement in clinical outcomes (hospital stay, recovery of FEV_1) among hospitalized patients for COPD exacerbations[14]. This study shows that a 5-day course of oral prednisolone is effective and non-inferior compared with the usually recommended 10–14 days courses in terms of reexacerbations for 6months. This study included an emergency department patient but this results could like to be generalized to outpatients with mild COPD grade. Although immediate steroid-related adverse events were not different in two groups, it is likely that shorter steroid treatment course will have an influence on risk of other steroid-related adverse events.

Management

Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Bateman et al.[15] Eur Respir J 2013;42:1484-94

We investigated the efficacy and safety of dual bronchodilation with QVA149 versus its monocomponents indacaterol and glycopyrronium, tiotropium and placebo in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). This was a multicentre, randomised, double-blind, placebo- and active-controlled, 26-week trial. Patients (n = 2144) were randomised (2:2:2:2:1) to receive once-daily QVA149 (indacaterol 110 μg/glycopyrronium 50 μg), indacaterol 150 μg, glycopyrronium 50 μg, open-label tiotropium 18 μg or placebo. The primary end-point was trough forced expiratory volume in 1 s (FEV1) at week 26 for QVA149 versus its monocomponents. Secondary end-points included dyspnoea, health status, rescue medication use and safety. Trough FEV1 at week 26 was significantly improved (p<0.001) with QVA149 compared with indacaterol and glycopyrronium (least squares mean (LSM) differences 0.07 L and 0.09 L, respectively), tiotropium and placebo (LSM differences 0.08 L and 0.20 L, respectively); these beneficial effects were sustained throughout the 26-week study. QVA149 significantly improved dyspnoea and health status versus placebo (p<0.001 and p = 0.002, respectively) and tiotropium (p = 0.007 and p = 0.009, respectively) at week 26. All treatments were well tolerated. Dual bronchodilation with once-daily QVA149 demonstrated superior and clinically meaningful outcomes versus placebo and superiority versus treatment with a single bronchodilator, with a safety and tolerability profile similar to placebo, supporting the concept of fixed-dose long-acting muscarinic antagonist/long-acting β2-agonist combinations for the treatment of COPD. *(Bateman et al.[15]; Reproduced with permission of the European Respiratory Society ⓒ. Eur Respir J May, 2013,42:1484-1494; doi:10.1183/09031936.00200212)*

1. Comments

Current guidelines recommend treatment with one or more long-acting bronchodilator for patients with moderate or more severe COPD. Compared with tiotropium monotherapy, indacaterol plus tiotropium promoted greater bronchodilation and lung deflation with no additional safety signal[16]. QVA149, an inhaled combination of two 24-hour bronchodilators, the LABA indacaterol and the LAMA glycopyrronium, is in development for COPD. QVA149 demonstrated fast and continued bronchodilation with significant improvements compared with indacaterol monotherapy and placebo in COPD patients[17]. This study shows that additional effect of indacaterol and glycopyrronium in a combination device as dual bronchodilator sustains over 24 hours. The previous ILLUMINATE study showed that once-daily QVA149 provides significant, sustained, and clinically meaningful improvements in lung function and symptomatic benefit compared with twice-daily salmeterol-fluticasone[18]. These results indicate the potential of dual bronchodilation as a treatment option for non-exacerbating symptomatic COPD patients. It can be used as single bronchodilator in patients with GOLD group B to D of COPD. This study shows that QVA149 is superior in clinical end points over tiotropium which is currently recommeded standard treatment in patients with GOLD groups of COPD. A limitation of this study was that it did not include all severity of COPD and excluded a recent COPD exacerbation unlike SPARK study[19].

Tiotropium Respimat inhaler and the risk of death in COPD. Wise et al.[20] N Engl J Med 2013;396:1491-501

BACKGROUND: Tiotropium delivered at a dose of 5 μg with the Respimat inhaler showed efficacy similar to that of 18 μg of tiotropium delivered with the HandiHaler inhalation device in placebo-controlled trials involving patients with chronic obstructive pulmonary disease (COPD). Although tiotropium HandiHaler was associated with reduced mortality, as compared with placebo, more deaths were reported with tiotropium Respimat than with placebo.
METHODS: In this randomized, double-blind, parallel-group trial involving 17,135 patients with COPD, we evaluated the safety and efficacy of tiotropium Respimat at a once-daily dose of 2.5 μg or 5 μg, as compared with tiotropium HandiHaler at a once-daily dose of 18 μg. Primary end points were the risk of death (noninferiority study, Respimat at a dose of 5 μg or 2.5 μg vs. HandiHaler) and the risk of the first COPD exacerbation (superiority study, Respimat at a dose of 5 μg vs. HandiHaler). We also assessed cardiovascular safety, including safety in patients with stable cardiac disease.
RESULTS: During a mean follow-up of 2.3 years, Respimat was noninferior to HandiHaler with respect to the risk of death (Respimat at a dose of 5 μg vs. HandiHaler: hazard ratio, 0.96;

95% confidence interval [CI], 0.84 to 1.09; Respimat at a dose of 2.5 μg vs. HandiHaler: hazard ratio, 1.00; 95% CI, 0.87 to 1.14) and not superior to HandiHaler with respect to the risk of the first exacerbation (Respimat at a dose of 5 μg vs. HandiHaler: hazard ratio, 0.98; 95% CI, 0.93 to 1.03). Causes of death and incidences of major cardiovascular adverse events were similar in the three groups.

CONCLUSIONS: Tiotropium Respimat at a dose of 5 μg or 2.5 μg had a safety profile and exacerbation efficacy similar to those of tiotropium HandiHaler at a dose of 18 μg in patients with COPD. *(Wise et al.[20], 2013, p. 1491; Reprinted with permission of Massachusetts Medical Society)*

1. Comments

The UPLIFT trial showed that Tiotropium Handihaler did not report any increase in mortality or cardiovascular events but previous meta-analysis shows that Tiotropium delivered with the Respimat SoftMist Inhaler is associated with significant increased risk of mortality and cardiovascular death in patient with COPD compared with placebo[21]. These concerns about the cardiac safety of anticholinergics was continuing debate and the subgroup of COPD Respimat group with known rhythm and cardiac disorders at baseline had an especially high risk for cardiac death[22]. This TIOSPIR trial shows that Tiopropium Respimat inhaler is not associated with a higher risk of mortality than Tiotropium Handihaler. Time to first exacerbation seem to be the same for patients receiving 2.5 μg or 5 μg Tiotropium Respimat inhaler and Handihaler group. A limitation of this study was that patients with a myocardial infarction within 6 months, hospitalization for heart failure within 12 months or unstable or life-threatening arrhythmia, moderate-to-severe renal failure were excluded from enrollment in the TIOSPIR trial.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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