FREQUENT EXACERBATORS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: FROM RESEARCH TO CLINICAL PRACTICE

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ABSTRACT

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are major causes of morbidity and mortality and contribute to disease progression. The frequency with which COPD patients experience exacerbations can differ markedly between patients, even those with a similar severity of airflow obstruction. This has led to the concept of 'frequent exacerbators' that represent a unique phenotype of COPD patients who experience frequent exacerbations and have poorer outcomes compared with patients with infrequent exacerbations. However, the mechanisms whereby some COPD patients experience frequent exacerbations remain undetermined. Understanding the mechanisms of frequent exacerbations will lead to the development of new therapies that can be targeted to these high-risk patients, thereby reducing exacerbations and improving outcomes.

Keywords: Chronic obstructive pulmonary disease (COPD), exacerbations, frequent exacerbators, biomarkers.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and is the fourth leading cause of mortality worldwide.[1] The clinical course of COPD is characterised by a progressive decline in lung function and worsening health status that is punctuated by periods of increased symptoms that are termed 'acute exacerbations'.[2] Acute exacerbations are the major contributors to morbidity, mortality, and excess healthcare costs in COPD, and often result in unscheduled healthcare visits, excess medication use, and hospitalisations. Exacerbations also have long-term effects beyond the acute episode as they are associated with faster decline in lung function, airway and systemic inflammation, and impaired quality of life.[3,5] Therefore, prevention of exacerbations is a major therapeutic goal in COPD. Although acute exacerbations are common not all COPD patients have the same frequency of exacerbations, with some experiencing a higher than average number of exacerbations. This brief review analyses the evidence for a frequent exacerbator phenotype and reviews the recent studies that have investigated the effects of treatments in this group of COPD patients.

DEFINING FREQUENT EXACERBATORS

The term 'frequent exacerbators' was first used in 1998 in a study from the East London COPD cohort examining the effects of exacerbations on quality of life (QoL) in COPD patients.[5] The median number of exacerbations was 3 per patient per year, and this was taken as a cut-off point to divide the patients into infrequent exacerbators (≤2 exacerbations per year) and frequent exacerbators (≥3 exacerbations per year) groups. Using the St George Respiratory Questionnaire (SGRQ) patients with frequent exacerbations were found to have worse QoL compared with patients with infrequent exacerbations. The study also reported that frequent exacerbations in the

previous year and daily respiratory symptoms were predictive of frequent exacerbators. Since this initial publication there have been a number of studies examining the effects of frequent exacerbations, although not all these studies have used the same definition of frequent exacerbators.[4,6-8] The definition of frequent exacerbators has varied between studies as the definition of exacerbations themselves remains problematic. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines an acute exacerbation as an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication.[9] This definition is adequate for clinical purposes but for epidemiological and research purposes it lacks precision. The assessment that a patient's symptoms are worse than usual fluctuations remains a subjective judgement both on the part of the patient and the healthcare provider. In addition, other medical conditions that commonly co-exist in COPD patients, such as congestive cardiac failure, pneumonia, and pulmonary embolism, also result in increased symptoms and therefore would be encompassed by such a definition.

Another major area of contention is the requirement for a change in medication. Some studies only include exacerbations that require treatment with antibiotics and/or oral corticosteroids, whereas others include all events experienced by patients irrespective of whether they require systemic treatment. In a cohort of COPD patients keeping daily diary cards of respiratory symptoms the rate of reported exacerbations was 0.8 per person per year, but the rate of exacerbations identified from the diaries was 2.7 per person per year.[10] Other studies have confirmed high rates of exacerbations that are experienced by patients but not reported to healthcare providers and are therefore not treated.[10,11] As a consequence, the rate of exacerbations in COPD patients will differ markedly depending on how exacerbations are defined and this in turn will influence which patients are defined as frequent exacerbators. Therefore, it is not surprising that there are discrepancies between studies on the prevalence and characteristics of frequent exacerbators that are highlighted in this review, when the definition of exacerbations is so variable. Symptom questionnaires such as the EXAcerbations of Chronic pulmonary disease Tool (EXACT)[12] and the COPD Assessment Tool (CAT)[13] are currently being validated as tools to provide more objective measures with which to define exacerbations. Future studies using such patient-reported outcome tools may lead to more objective definitions of exacerbations, further refinement of the definition of frequent exacerbators, and standardisation of definitions between different studies.

BIOMARKERS

The ongoing issues with the current subjective definitions of exacerbations have led to considerable interest in the role and utility of biomarkers. Identification of objective markers that can stratify COPD patients into either frequent or infrequent exacerbators offers the prospect of removing the uncertainty that surrounds the correct definition of exacerbations. A number of studies have identified relationships between inflammatory markers and exacerbation frequency in COPD patients. Six inflammatory biomarkers (C-reactive protein [CRP], white blood cell [WBC] count, interleukin 6 [IL-6], IL-8, fibrinogen, and tumour necrosis factor alpha) were analysed over a 3-year period in 1,755 COPD patients.[14] A subgroup of COPD patients (16%) demonstrated persistent systemic inflammation with ≥2 biomarkers (WBC count, CRP, IL-6, or fibrinogen) in the upper quartile distribution after 1-year follow-up, which was associated with an increased exacerbation frequency (1.5 versus 0.9 per year, $p<0.001$) and increased all-cause mortality (13% versus 2%, $p<0.001$). In a cohort of 6,574 COPD patients there was a stepwise increase in the risk of exacerbation from no baseline elevated biomarkers through to three high baseline inflammatory biomarkers: CRP (>3 mg/l), fibrinogen (>14 µmol/l), and WBC count (>9 x 10^9/l). The odds ratio (OR) for having frequent exacerbations in the first follow-up year was 3.7 (95% confidence interval: 1.9-7.4; 81 events/1,000 person-years) for individuals with elevated levels of all three biomarkers, compared with no elevated biomarkers (9 events/1,000 person-years).[15] Moreover, these markers identified an increased risk of exacerbation even in patients with no previous exacerbations. Frequent exacerbations are also associated with a greater increase in inflammatory markers over time. In a cohort of 148 patients with moderate to severe COPD, patients classified as frequent exacerbators (≥2.52 exacerbations per year) demonstrated a faster rise over time in baseline plasma fibrinogen and sputum IL-6.[3] Future studies will aim to determine the best

biomarker or combination of biomarkers, and how these can be best combined with clinical parameters to identify exacerbation risk in individual COPD patients.

EVALUATION OF COPD LONGITUDINALLY TO IDENTIFY PREDICTIVE SURROGATE ENDPOINTS

The largest and most comprehensive study of exacerbation frequency was from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort that enrolled 2,138 COPD patients and followed them over a period of 3 years.[16] Exacerbations were defined as events that led a healthcare provider to prescribe antibiotics or corticosteroids (or both), or that resulted in hospitalisation. Frequent exacerbators were defined as patients with ≥2 exacerbations per year, and infrequent exacerbators as those with <2 exacerbations per year. A relationship between exacerbation frequency and airflow obstruction was identified, with 22% of GOLD Stage II (moderate) patients experiencing frequent exacerbations compared with 47% of GOLD Stage IV (very severe) patients. However, disease severity is not the sole determining factor of exacerbation frequency, as up to a one-fifth of patients with moderate COPD experience frequent exacerbations and less than half of patients with very severe COPD are frequent exacerbators. The study also examined whether the occurrence of exacerbations remained stable over the 3-year study period. Of the 1,187 infrequent exacerbators during Year 1, 987 had <2 exacerbations in Year 2 (negative predictive value: 83%). Among the 492 patients with frequent exacerbations in Year 1, 296 had ≥2 exacerbations in Year 2 (positive predictive value: 60%). Thus, exacerbation frequency in the first year had a sensitivity of 60% and a specificity of 83% for the frequency in the second year. Over the whole 3-year study period 296 patients had frequent exacerbations in both Year 1 and Year 2, and of these 210 (71%) had frequent exacerbations in Year 3. There were 521 patients who had no exacerbation in both Year 1 and Year 2, and 388 (74%) of these also had no exacerbation in Year 3. Therefore, the authors suggest that the relative stability of exacerbation status over time warrants the description of a phenotype within COPD. The study also analysed the factors associated with frequent exacerbations and found that reduced lung function, poorer health status, a history of gastro-oesophageal reflux disease (GORD), and an increased WBC count were independently associated with frequent exacerbations.

OTHER STUDIES

Since the publication of the ECLIPSE study other studies have investigated the characteristics and prevalence of frequent exacerbators among COPD patients. Wan et al.[7] investigated 345 subjects with COPD GOLD Stages III and IV and defined frequent exacerbations as ≥2 exacerbations in the last year, or ≥4 exacerbations over the preceding 24 months with at least one exacerbation in the last year.[17] Significant clinical predictors of frequent exacerbator status were physician-diagnosed asthma, Medical Research Council dyspnoea score, and forced expiratory flow 25-75% predicted, but there was no relationship with current tobacco use, forced expiratory volume (FEV_1) percentage predicted, or previous exacerbation history. Another study of 121 patients with moderate to severe COPD defined frequent exacerbations as ≥2 exacerbations per year.[18] SGRQ total score and a course of oral corticosteroid within 3 months prior to the study together predicted best whether patients would be infrequent or frequent exacerbators over the course of the next year, but previous exacerbation history was not associated with exacerbation status. Unlike the ECLIPSE cohort there did not appear to be stability of exacerbator status as 58% of frequent exacerbators had <2 exacerbations in the previous year. A Chinese study of 227 patients identified lung function, comorbidities, and acute respiratory failure as predictors of frequent exacerbators.[19] A post-hoc analysis of the POET study[20] (Prevention of Exacerbations with Tiotropium in COPD) analysed data from 7,376 patients enrolled in a clinical trial of tiotropium. Patients were classified as non-exacerbators (63.5%), infrequent exacerbators (1 exacerbation, 22.9%), and frequent exacerbators (≥2 exacerbations, 13.6%). Similar to the ECLIPSE cohort, patients with frequent exacerbations tended to have more severe disease and treatment with ≥2 antibiotic or corticosteroid courses in the previous year. Other factors associated with frequent exacerbations were more pulmonary medication at baseline, female sex, and ex-smokers. Compared with ECLIPSE the proportion of patients classed as frequent exacerbators was considerably less (11.6% in GOLD Stage II patients and 15.6% in GOLD Stages III/IV). A database study of COPD patients in primary care in the UK reported that

20% of patients with FEV_1 >50% predicted and 30% of patients with FEV_1 <50% predicted had ≥2 exacerbations in the previous year.[21] By contrast, in a COPD cohort from Denmark, <2% of patients with FEV_1 >50% predicted and <10% of patients with FEV_1 <50% predicted had ≥2 exacerbations in the previous year.[22] An analysis of the patients in the ECLIPSE cohort who had different exacerbation frequencies from one year to the next failed to identify factors that could predict a change in exacerbator status.[23]

Therefore, different studies have had varying results with regards to the factors associated with frequent exacerbations, the stability of exacerbator phenotype over time, and the prevalence of frequent exacerbators in COPD populations. This is likely to be related to different definitions of frequent exacerbators, variations in study design and analysis, and different study populations. Despite these discrepancies the latest GOLD consensus report proposed a new staging system for COPD that incorporates exacerbation frequency as a component.[9] Whereas previously severity staging was based on lung function only, the new system characterises patients as high or low risk based on spirometry and exacerbation frequency. The high-risk patients (groups C and D) are defined as those with FEV_1 <50% predicted or ≥2 exacerbations in the previous year. It appears that this new staging system is not superior to the previous spirometry-based system in predicting hospitalisations and mortality,[24] one study has reported it to be inferior,[25] and therefore debate continues as to its validity.[26]

CONSEQUENCES OF FREQUENT EXACERBATIONS

Studies have identified associations between frequent exacerbations and a number of important outcomes in COPD, including faster decline in lung function,[4,27,28] impaired health status and depression,[5,7] reduced activity,[29] bacterial colonisation,[30] and systemic[3] and airway inflammation.[3,31] In the POET study frequent exacerbators constituted 13.6% of the population but accounted for 56.6% of exacerbation-related hospitalisations.[20] Thus, these studies highlight associations between frequent exacerbations and poor outcomes but they are unable to identify the direction of the relationship. It is not clear whether frequent exacerbations cause these outcomes, whether these factors contribute to the occurrence of frequent exacerbations, or whether they are markers of a COPD phenotype with no causal relationship. This has important clinical implications: if exacerbations cause poorer outcomes, then targeting these patients to reduce exacerbations will have therapeutic benefits.

THERAPEUTIC IMPLICATIONS

It is well established that inhaled therapies for the management of COPD, including inhaled corticosteroids (ICS), long-acting beta-2 agonists, and long-acting muscarinic antagonists (LAMAs) reduce the frequency of acute exacerbations.[32,33] Most of these studies were published prior to the description of frequent exacerbators and therefore it is not known whether the effects of treatments differ between patients with different exacerbation frequencies. Recent post-hoc analyses of previously published studies and new research have specifically examined the effects of treatments in subgroups of COPD patients according to exacerbation frequency.

ROFLUMILAST

Phosphodiesterase-4 (PDE-4) is an enzyme expressed in a range of inflammatory cells that catalyses the breakdown of cyclic adenosine monophosphate (cAMP), a second messenger molecule with immunomodulatory activity.[34] Inhibition of PDE-4 results in higher levels of cAMP, which acts to suppress the activity of immune and inflammatory cells. In a small, crossover, placebo-controlled study the PDE-4 inhibitor roflumilast resulted in a 35-50% reduction in the number of inflammatory cells in sputum of COPD patients.[35]

A post-hoc analysis of pooled data from two placebo-controlled, double-blind, multi-centre studies has shown that roflumilast can shift patients from a frequent to an infrequent exacerbator phenotype.[36] Symptomatic subjects with GOLD Stage III or IV COPD were randomly assigned to receive roflumilast or placebo for 1 year in studies M2-124 and M2-125.[37] Participants did not use ICS or LAMAs during the study period but continued all other standard therapies and the annual rates of exacerbations were assessed at study entry and after 1 year of treatment. In total 3,091 patients were analysed of which 830 (27%) were frequent exacerbators (≥2 exacerbations in the previous year). In the frequent exacerbators treated with roflumilast, 32% continued to have frequent

exacerbations, compared with 40.8% of those taking placebo at the end of 1 year. The risk of remaining in the frequent exacerbator group when treated with roflumilast was reduced by 20% compared with placebo, a risk ratio of 0.799. This effect on exacerbations was most evident for those with GOLD Stage III COPD, although numbers were smaller in the GOLD IV group. An interesting observation from this study was that 59.2% of the frequent exacerbators who received placebo did not have frequent exacerbations over the year of the study, suggesting that exacerbation frequency can be influenced by non-pharmacological interventions such as frequent patient monitoring that was part of the study protocol. The GOLD guidelines recommend the use of roflumilast to reduce exacerbations in patients with chronic bronchitis and FEV_1 <50% predicted.[9]

AZITHROMYCIN

Azithromycin is a macrolide antibiotic that possesses anti-inflammatory and immunomodulatory properties in addition to its antibacterial activity. A randomised, placebo-controlled trial has evaluated the use of azithromycin in reducing frequency of exacerbations in COPD patients.[38] The investigators randomised 1,142 subjects to receive a daily 250 mg dose of azithromycin or placebo for 1 year in addition to their standard treatment. The median time to first exacerbation was greater (266 days versus 174 days, p<0.001) and the frequency of acute exacerbations was lower (1.48 versus 1.83 exacerbations per patient-year, p<0.001 in those receiving azithromycin compared with placebo. A Cochrane systematic review of seven randomised controlled trials published between 2001 and 2011 concluded that continuous use of prophylactic macrolide antibiotics resulted in a clinically significant reduction in exacerbation rates in patients with at least moderate COPD.[39]

The COLUMBUS trial[40] was a randomised, double-blind, placebo-controlled study from the Netherlands that examined the effect of macrolide treatment in COPD patients with frequent exacerbations (≥3 exacerbations treated in the previous year). A total of 92 patients were randomly assigned to receive 500 mg azithromycin or placebo three times per week for 1 year. There were 84 exacerbations in the azithromycin group compared with 129 in the placebo group. After adjustment for covariates, the exacerbation rate ratio of azithromycin compared with placebo was 0.58 (p=0.001). The median time with first exacerbation was also greater in the azithromycin group compared with placebo (130 days versus 59 days, p=0.001). Concerns remain regarding the emergence of antibiotic resistance with long-term antibiotic use and current international guidelines do not recommend use of prophylactic azithromycin in COPD.[9]

N-ACETYLCYSTEINE

Exogenous and endogenous oxidative stress plays a central role in the pathogenesis of COPD, and increased oxidative stress and oxidant—antioxidant imbalance has been demonstrated in COPD patients.[41] Reduced levels of the antioxidant glutathione have been associated with increased risk of COPD exacerbations.[42] N-acetylcysteine (NAC) is a mucolytic agent that also has antioxidant effects by acting as a precursor of the antioxidant glutathione and a free radical scavenger.[43] NAC has been shown to reduce markers of oxidative stress in COPD[44] and a number of studies have evaluated its effect on clinical outcomes in COPD. The Bronchitis Randomised on NAC Study (BRONCUS) was a 3-year, double-blind, randomised, placebo-controlled trial of low-dose NAC (600 mg once daily) in COPD subjects with ≥2 exacerbations in the last year. NAC had no effect on the annual rate of decline in FEV^1 or the number of exacerbations, but subgroup analysis suggested that the exacerbation rate was reduced in patients not treated with ICS.[45] A study of higher-dose NAC (600 mg twice daily) carried out in Chinese patients did report a reduction in exacerbations with NAC.[46] A subsequent post-hoc subgroup analysis analysed the effects of NAC separately in high-risk (GOLD categories C and D) versus low-risk patients (GOLD categories A and B).[47] There were 89 patients classified as high risk of which 83.1% had suffered ≥2 exacerbations in the past year. In the high-risk group, the cumulative exacerbation frequency at 1 year was 1.08 with NAC, compared with 2.22 with placebo (p=0.04). Furthermore, mean time to first exacerbation was longer with NAC compared with placebo (258.2 days versus 203.6 days, p=0.02), and the proportion of exacerbation-free patients at 1 year was 51.3% with NAC compared with 24.4% with placebo (p=0.013). The effects of NAC on exacerbations remained significant if patients were stratified on the basis of frequent exacerbator

phenotype alone. The beneficial clinical effects of NAC were not seen in those patients classified as low risk.

ANTI-REFLUX TREATMENT

Symptoms of gastro-oesophageal reflux are common in COPD patients and associated with exacerbations;[48] the ECLIPSE study identified GORD as a risk factor for frequent exacerbations in COPD patients.[16] This association was also identified in a subsequent independent cohort of COPD patients.[49] The association would suggest that anti-reflux therapy may be beneficial in COPD patients if the relationship between GORD and exacerbations is causal, but to date there has only been a single study of anti-reflux therapy in COPD. In a randomised, observer-blind trial over 1 year 100 Japanese patients with COPD were randomly assigned to conventional COPD therapy or conventional therapy plus the proton pump inhibitor lansoprazole 15 mg daily.[50] The number of exacerbations was lower in those receiving lansoprazole compared with controls (0.34 versus 1.18, $p<0.001$) and the OR of having ≥1 exacerbation per year with lansoprazole compared with controls was 0.23 ($p=0.004$). However, there were imbalances in baseline characteristics between the subjects assigned to the two groups. Patients assigned to the placebo group had significantly more exacerbations per year (1.18±1.4 versus 0.34±0.72, $p<0.001$) and there were more patients with ≥1 exacerbations per year (52% versus 24%, $p=0.004$) compared with the treatment group. Therefore, the placebo group were at higher risk of exacerbation and the results may be attributed to this rather than a true therapeutic effect of lansoprazole. The lack of patient blinding also raises the possibility of a placebo effect. Larger double-blind studies with equal exacerbation risk between treatment arms are required to elucidate the role of anti-reflux therapy as an intervention to reduce exacerbations.

NON-PHARMACOLOGICAL THERAPIES

Non-pharmacological interventions such as pulmonary rehabilitation have beneficial effects on a number of outcomes in COPD including exacerbations, although this has not been reported in all studies. A Dutch group studied the effects of a comprehensive pulmonary rehabilitation programme on exacerbation frequency in 343 COPD patients with a high self-reported exacerbation rate (>3 exacerbations in the previous year).[51] The mean number of exacerbations decreased from 4.56±3.26 in the year prior to the pulmonary rehabilitation to 3.18±2.53 in the year following, with a significant decrease in hospitalisations. 69% of the participants had ≥2 exacerbations in the previous year, whereas during the year following pulmonary rehabilitation 54% of patients experienced frequent exacerbations. This was not a randomised trial and comparison was made with historical controls, thus it cannot prove conclusively that pulmonary rehabilitation reduces exacerbation frequency. Further randomised, prospective studies of non-pharmacological interventions in frequent exacerbators are warranted.

FUTURE DEVELOPMENTS AND RESEARCH

The description of a subset of COPD patients who experience frequent exacerbations has been widely accepted and incorporated into the updated GOLD system for COPD assessment. The description of this patient group as a phenotype implies the existence of an underlying mechanism (or mechanisms) determining susceptibility to exacerbations. The mechanism(s) of frequent exacerbations remain undetermined but possible candidates include susceptibility to respiratory infections, an altered respiratory microbiome, gastro-oesophageal reflux, psychosocial factors including symptom perception, depression and anxiety, and social support and medication adherence.[52] Although a number of studies have described the frequent exacerbator phenotype, no progress has been made in elucidating the underlying mechanisms. Such diverse potential mechanisms require radically different treatment approaches; therefore, the rational development of new therapies targeted at frequent exacerbators can only occur with an improved understanding of the underlying mechanisms. It is likely that there is not a single mechanism but that multiple mechanisms exist and that in the future the frequent exacerbator phenotype will be further refined according to underlying cause. Future research will need to examine each of these specific hypotheses to determine the key mechanisms of frequent exacerbations so that novel treatments targeting these pathways can be developed in order to reduce the burden of disease associated with COPD exacerbations.

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