How Phosphodiesterase 4 Inhibitors Work in Patients with Chronic Obstructive Pulmonary Disease of the Severe, Bronchitic, Frequent Exacerbator Phenotype

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KEYWORDS

• Phosphodiesterase 4 inhibitors • Roflumilast • COPD phenotypes • Gene transactivation
• Combination therapies • Acute exacerbations

KEY POINTS

- The novel, antiinflammatory drug, roflumilast, is efficacious in patients with severe chronic obstructive pulmonary disease (COPD) who have chronic bronchitis and a history of frequent exacerbations.
- This COPD phenotype is associated with mucus hypersecretion, an increased risk of bacterial colonization and infection, and a high level of inflammation. Such patients are most likely to derive clinical benefit from antiinflammatory drugs, such as the phosphodiesterase 4 inhibitor, roflumilast.
- The antiinflammatory benefit of roflumilast alone and in the presence of an inhaled corticosteroid/long-acting β_2-adrenoceptor agonist combination therapy may be caused, in part, by the de novo expression of a variety of antiinflammatory genes.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an umbrella term that describes a heterogeneous collection of distinct, debilitating, pulmonary-related disorders that, in many individuals, coexist. COPD is defined clinically by a progressive and largely irreversible decrement in expiratory airflow[1] that is often associated with airway collapse, fibrosis, edema, mucus hypersecretion, airway and systemic inflammation, skeletal muscle wasting, pulmonary hypertension, right sided heart failure, and venous thromboembolism. The variable extent to which an individual presents with one or more of these clinical

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entities accounts for the wide spectrum of disease seen in clinical practice. COPD typically affects middle-aged and elderly people, and it is a general perception that chronic cigarette smoking is the primary cause.[2,3] However, long-term exposure of individuals to biomass fuel combustion products, used largely in the process of indoor cooking, also is now recognized as a significant cause especially in developing countries.[4]

COPD heterogeneity is probably caused by a complex interplay between genetic factors, which remain largely indeterminate, and the environment, in which tobacco smoke and pollutants are primary players.[5–8] It is intuitive that phenotypic diversity of COPD precludes effective treatment. Because current pharmacotherapies were not rationally designed to target distinct phenotypes, the current one-size fits all approach to management is inherently flawed and poorly effective. Therefore, although COPD heterogeneity is problematic, it nevertheless creates potential opportunities for the design of therapies tailored to the phenotype of interest.[9] In 2012, 4 broad COPD clinical phenotypes (denoted A–D) were proposed based on prognostic and therapeutic relevance (**Fig. 1**A).[10,11] According to this taxonomy, which is distinct from the groups defined in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (see **Fig. 1**B; www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf), patients are categorized as having infrequent exacerbations (A), an asthma/COPD overlap (B), exacerbations with emphysema (C), or exacerbations with chronic bronchitis (D). This article focuses on patients of the D phenotype. These patients have severe disease (GOLD stage 3–4), present with a history of productive cough or expectoration (>3 months per year and for more than 2 consecutive years) and respond to the novel, antiinflammatory drug, roflumilast (marketed variably as Daxas, Daliresp, and Libertek). Frequent exacerbations of COPD are associated, maybe causally, with mucus hypersecretion, an increased risk of bacterial colonization and infection, and a high level of inflammation.[12] Together, these characteristics suggest that patients of a severe, bronchitic phenotype are most likely to derive clinical benefit from antiinflammatory drugs, such as the phosphodiesterase (PDE) 4 inhibitor, roflumilast. A post hoc analysis of 2 phase III studies (AURA, M2-124; HERMES, M2-125[13]) found that roflumilast (500 μg daily for 1 year) transformed patients classified as frequent exacerbators at the outset of the trial into a more stable, infrequent exacerbator phenotype.[14]

PDE4 INHIBITORS AND COPD

PDEs represent a superfamily of enzymes that degrade the second messenger molecules cyclic adensosine-3′,5′-monophosphate (cAMP) and/or cyclic guanosine-3′,5′-monophophate to the catalytically inactive, corresponding 5′-nucleoside monophosphates. Following the first identification of a PDE activity more than 50 years ago,[15] 11 molecularly, biochemically, and immunologically distinct enzyme families have been clearly

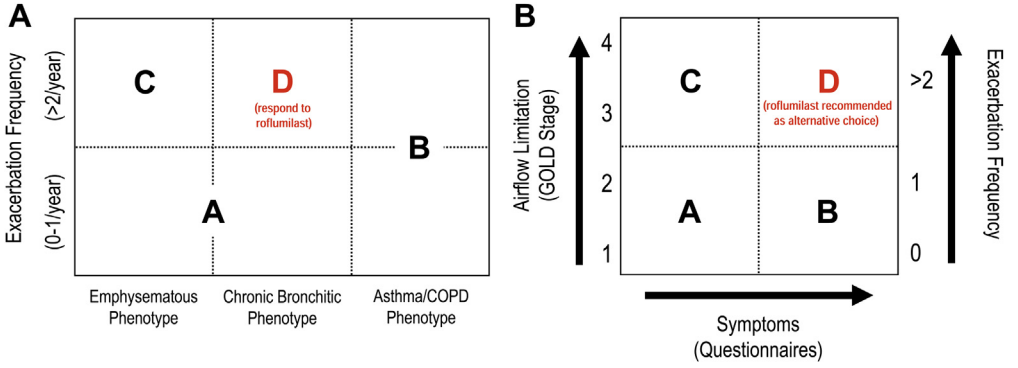

Fig. 1. Classification of COPD. (*A*) The subdivision of COPD into 4 broad phenotypes wherein patients are categorized as having infrequent exacerbations (A), an asthma/COPD overlap (B), exacerbations with emphysema (C), or exacerbations with chronic bronchitis (D). (*B*) The Global Initiative for Chronic Obstructive Lung Disease classification of COPD, which is based on airflow limitation, exacerbation history, and symptoms (determined by questionnaire). Patients are classified as low risk, fewer symptoms (A), low risk, more symptoms (B), high risk, fewer symptoms (C), or high risk, more symptoms (D). The phosphodiesterase (PDE) 4 inhibitor, roflumilast, is a recommended treatment option for group D patients in both classifications (shown in red). (*Adapted from* Miravitlles M, Jose Soler-Cataluna J, Calle M, et al. Treatment of COPD by clinical phenotypes. Putting old evidence into clinical practice. Eur Respir J 2013;41(6):1252–6.)