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Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping

Paolo Montuschi[1], Mario Malerba[2], Giuseppe Santini[1] and Marc Miravitlles[3]

[1] Department of Pharmacology, Faculty of Medicine, University Hospital Agostino Gemelli, Catholic University of the Sacred Heart, Rome, Italy
[2] Department of Internal Medicine, Spedali Civili di Brescia, University of Brescia, Italy
[3] Pneumology Department, Hospital Universitari Vall d'Hebron, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

Chronic obstructive pulmonary disease (COPD) is characterized by large phenotype variability, reflected by a highly variable response to pharmacological treatment. Nevertheless, current guidelines suggest that patients with COPD of similar severity should be treated in the same way. The phenotype-based pharmacotherapeutic approach proposes bronchodilators alone in the nonfrequent exacerbator phenotype and a combination of bronchodilators and inhaled corticosteroids in patients with asthma–COPD overlap syndrome (ACOS) and moderate-to-severe exacerbator phenotype. The clinical importance of phenotypes is changing the paradigm of COPD management from evidence-based to personalized medicine. However, the personalized pharmacological strategy of COPD has to be validated in future clinical studies.

Introduction

The history of the guidelines for COPD treatment is an example of the simplification of a complex reality. The Venn diagram included in the American Thoracic Society (ATS) statement for management of COPD in 1995 reflected the complexity of the disease and its different clinical presentations [1]. However, the limited alternatives for pharmacological treatment at that time made it unnecessary to identify the different types of patient for clinical practice. The evolution of the one-treatment-fits-all concept led to the selection of the pharmacological treatment based almost exclusively on the severity of airflow obstruction introduced in the Global Obstructive Lung Disease (GOLD; http://www.goldcopd.com) document in 2001 [2] and following revisions up to 2011. The 2011 GOLD guidelines and its revisions changed the paradigm, proposing a pharmacological treatment based on intensity of symptoms, as measured by the modified Medical Research Council (mMRC) dyspnea scale and/or the COPD Assessment Test, and risk of poor outcomes (identified by the degree of airflow obstruction and the frequency of exacerbations) in a 3D evaluation (GOLD) [3]. This was a significant step forward in considering the patient as a whole rather than only on the basis of the degree of airflow limitation; nevertheless, there is no mention in the current guidelines of differential pharmacological treatment based on clinical patient characteristics.

The past decade has seen an exponential increase in COPD research and new therapeutic options have been successfully developed [4], together with new use of old drugs in subgroups of patients with COPD [5]. It is now clear that not all patients respond equally to all drugs (irrespective of symptom severity and/or the level of risks), and identifying 'responders' is crucial [6,7]. In this context, the concept of a clinical phenotype in COPD has emerged as 'those attributes of the disease alone or in combination that describe the differences between individuals with COPD in relation to parameters that have clinical significance (symptoms, exacerbations, response to pharmacological treatment, rate of disease progression, or death)' [8]. The phenotype should be able to classify patients into subgroups with prognostic value and to determine the most appropriate therapy to achieve better results from a clinical standpoint. This constitutes the basis of a personalized approach to the pharmacological treatment of COPD.

Corresponding author:. Montuschi, P. (pmontuschi@rm.unicatt.it)

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Clinical COPD phenotypes

Previous studies have attempted to identify and quantify the prevalence of different COPD phenotypes, using populations of various sources, severities, and characteristics [9]. The objective is the identification and description of some phenotypes that have not only biological or epidemiological meaning, but also prognostic and therapeutic value, especially at the individual patient level.

The ATS Venn diagram already included all the clinical types of patient with COPD and their overlap [1]. Defining 'clinically relevant' phenotypes requires identifying those phenotypes that, besides determining clinical outcomes, also characterize patients with a different or selective response to specific pharmacological treatments and are prospectively validated. As an example, the fact that patients can present with predominant emphysema or chronic bronchitis [10] has therapeutic implications because only patients with chronic bronchitis (and exacerbations) can respond to roflumilast, a phosphodiesterase type 4 (PDE_4) inhibitor [4]. Therefore, identification of patients with the frequent exacerbation and chronic bronchitis phenotype is clinically relevant as well as identification of the frequent moderate-to-severe exacerbator and ACOS phenotype, which could have a greater response to inhaled corticosteroids (ICS).

Pharmacological treatment of the infrequent exacerbator phenotype

A flow chart of pharmacological treatment of COPD is shown in Box 1. Inhaled drugs and doses are shown in Table 1. The mechanism of action of bronchodilators is described in Box 2.

Pharmacotherapy of stable COPD can prevent and decrease symptoms (especially dyspnea), reduce exacerbation frequency and severity, and improve health status and exercise capacity (http://www.goldcopd.com). However, regular long-term treatment with bronchodilators does not alter the natural history of COPD and, therefore, no treatment is needed in patients who are asymptomatic.

Bronchodilators, administered via inhalation through pressurized metered dose inhalers (pMDI) or dry powder inhalers (DPI), are the mainstay of pharmacological treatment of the symptomatic infrequent exacerbator COPD phenotype. These drugs include long-acting muscarinic receptor antagonists (LAMA) and long-acting $beta_2$ agonists (LABA) [11,12].

Once-daily LAMA approved for COPD include tiotropium bromide and glycopyrronium bromide. Tiotropium bromide, a nonselective muscarinic receptor antagonist with a slow onset of bronchodilatation effect, was the first LAMA approved for COPD. Tiotropium is available as DPI at a dose of 18 μg daily and as soft mist inhaler at a dose of 2.5 μg two puffs daily [11]. Recently, glycopyrronium bromide and aclidinium bromide have also been approved [13,14]. They are both fast-acting bronchodilators with greater M_3 selectivity, but glycopyrronium bromide has a 24-hour duration of action, whereas aclidinium bromide requires twice daily administration because its bronchodilatating effect only lasts up to 12 hours [13,14]. Once-daily administration and M_3 selectivity are generally considered important achievements in the development of new LAMAs. However, recent data have challenged this paradigm. A 6-week phase IIIb study in patients with moderate-to-severe COPD showed that aclidinium, but not tiotropium, improved morning symptoms compared with placebo [15]. By contrast, M_2 receptor antagonism enhanced $beta_2$ agonist-induced airway relaxation in *in vitro* human airways [16]. LABAs approved for pharmacological treatment of COPD include salmeterol, formoterol and indacaterol [12]. Salmeterol, a partial agonist with a slow onset of action, and formoterol, a fast-acting full agonist, require twice-daily administration. Indacaterol, a fast-acting bronchodilator administered via a DPI in a single dose of 150 or 300 μg in Europe or 75 μg in the USA, has a 24-hour duration of action [12].

Several once-daily LABA, including olodaterol, vilanterol, milveterol, carmoterol, and abediterol, are in development [12]. Dual bronchodilatation with a fixed-dose combination (FDC) of LAMA and LABA is likely to be the most effective, whereas once-daily pharmacological treatment in patients with moderate-to-severe COPD with infrequent exacerbations, as suggested by the SHINE and ILLUMINATE studies [17,18]. Approved once-daily combinations include glycopyrronium bromide/indacaterol [19] and umeclidinium bromide/vilanterol [20] whereas once-daily tiotropium/olodaterol and twice-daily aclidinium/formorterol [21] are in clinical development. In addition, in addition, dual-pharmacology muscarinic antagonist and $beta_2$-agonist (MABA) molecules for COPD treatment are in clinical development [22] (http://www.astrazeneca-annualreports.com/2013).

Pharmacological treatment of the frequent exacerbator phenotype

The COPD frequent exacerbator phenotype, defined by the occurrence of two or more exacerbations per year [23,24], is based on clinical records and/or patient recall. Diagnosis based on patients reporting their history of exacerbations is reliable [25]. The COPD exacerbator phenotype implies a worse prognosis [26], underscores the importance of asking and recording the exacerbation history in the clinical record and identifies patients who might require anti-inflammatory treatment added to bronchodilators.

The COPD frequent exacerbator phenotype, clearly identified by the ECLIPSE study [23], can have predominant chronic bronchitis or emphysema [27]. Fixed-dose ICS/LABA combinations are recommended in patients with severe airflow limitation [forced expiratory volume in 1 s (FEV_1) < 50% predicted value) and two or more COPD exacerbations per year (http://www.goldcopd.com). Fixed-dose ICS/LABA/LAMA combinations, such as fluticasone furoate/vilanterol/umeclidinium bromide, for triple therapy are in development (http://www.gsk-clinicalstudyregister.com).

Chronic bronchitis, defined by the presence of productive cough or expectoration for more than 3 months a year and more than 2 consecutive years [28], has been associated with elevated risk of airway colonization and respiratory infection. This could explain why patients with chronic bronchitis have a higher exacerbation rate [28,29]. In these patients, ICS and, possibly, PDE_4 inhibitors [4], can be indicated on top of regular long-lasting bronchodilator treatment. Selected cases of frequent exacerbators might respond to long-term treatment with macrolides [5] and quinolones (particularly if they produce dark sputum) [30]. When ICS cannot be used, mucolytics might be effective in reducing exacerbations [31–33].

The frequent exacerbator with emphysema phenotype does not have chronic cough and sputum production, but has the typical clinical and radiological signs of emphysema [34]. The basis of pharmacological treatment in these patients is long-acting bronchodilators and, in some cases, ICS.

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