ELSEVIER

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)

1359-6446/06/$ - see front matter http://dx.doi.org/10.1016/j.drudis.2014.08.004

Please cite this article in press as: Montuschi, P. et al. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.08.004

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.

Please cite this article in press as: Montuschi, P. et al. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.08.004

BOX 1

Pharmacological treatment of COPD

Pharmacological treatment of COPD is based on a 3D evaluation including intensity of symptoms, degree of airflow limitation, and the frequency of exacerbations (http://www.goldcopd.com; Fig. 1). Bronchodilators, administered via inhalation through pMDI or DPI, are the mainstay of pharmacological treatment of the symptomatic infrequent exacerbator COPD phenotype. Bronchodilators for maintenance treatment of stable COPD include LAMA and selective LABA [11,12]. Once-daily LAMA approved for COPD include tiotropium bromide and glycopyrronium bromide, whereas aclidinium bromide requires twice-daily administration [11]. Umeclidinium bromide is a once-daily LAMA in phase III development for COPD [20]. Among LABA, indacaterol is suitable for once-daily administration [19], whereas salmeterol and formoterol require twice-daily administration [12]. New LABA under development for COPD include vilanterol, abediterol, milveterol and carmoterol [12]. Olodaterol received first approval for once-daily maintenance treatment of COPD [59]. FDC of LAMA/LABA is likely to be the most effective pharmacological treatment of patients with moderate-to-severe COPD with infrequent exacerbations [17,18]. Glycopyrronium/indacaterol and umeclidinium/vilanterol are approved for the once-daily maintenance treatment of COPD in some countries [19,20]. FDC of inhaled corticosteroids (ICS)/LABA are recommended in patients with severe airflow limitation (FEV_1 <50% predicted value) and two or more COPD exacerbations per year (http://www.goldcopd.com). ICS/LABA/LAMA FDC, such as fluticasone furoate/vilanterol/umeclidinium bromide, for triple therapy are in development (http://www.gsk-clinicalstudyregister.com). Oral roflumilast, a PDE_4 inhibitor, is indicated as an alternative therapeutic choice in patients with chronic bronchitis, severe airflow limitation (FEV_1 < 50% predicted value), and two or more COPD exacerbations per year on top of regular long-lasting bronchodilator or ICS/LABA treatment (http://www.goldcopd.com). The role of ICS in COPD is not well defined, as indicated by the fact that both ICS/LABA, FDC of anti-inflammatory drugs and long-lasting bronchodilators, and tiotropium, a long-lasting bronchodilator, as monotherapy, are equally considered as a first-choice treatment in patients with severe airflow limitation (FEV_1 < 50% predicted value) and two or more COPD exacerbations per year (http://www.goldcopd.com). This is particularly relevant because 25% of patients with COPD are reported to be overtreated with ICS, with negative consequences in terms of adverse effects, including increased risk of pneumonia, and costs associated with overuse [55]. When required, ICS in patients with COPD should always be administered as ICS/LABA FDC, not as monotherapy, as shown by the TOwards a Revolution in COPD Health (TORCH) study [58]. A comprehensive identification of subphenotypes of patients with COPD who are most likely to respond to ICS (e.g. ACOS or frequent exacerbator phenotype), also based on molecular fingerprinting obtained by 'omics platforms, could help define the role of these drugs in COPD and pave the way for implementing personalized pharmacological strategies. Dual MABA compounds combining both pharmacological activities in a single molecule are under development [22] (http://www.astrazeneca-annualreports.com/2013).

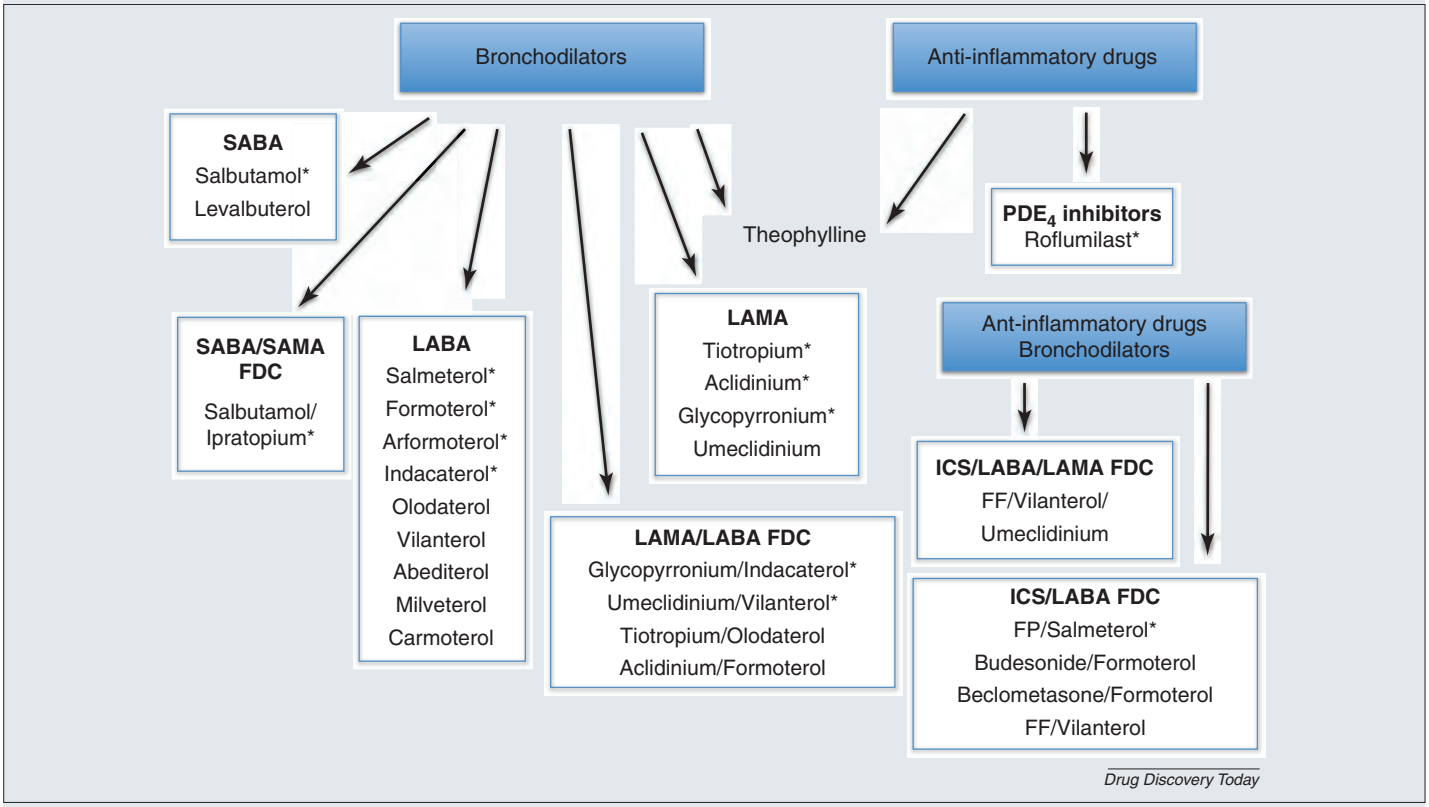

FIGURE 1

Flowchart for the treatment of stable chronic obstructive pulmonary disease (COPD). Drugs currently approved for COPD are signed with an asterisk. Abbreviations: FF, fluticasone furoate; FP, fluticasone propionate; SABA, short-acting $beta_2$-agonists; SAMA, short-acting muscarinic receptor antagonists. For additional abbreviations, see box and main.

Please cite this article in press as: Montuschi, P. et al. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.08.004

TABLE 1

Pharmacological characteristics of approved bronchodilators for COPD treatment[a,b]

Drug class	Active principle	Route of administration	Device: dose per puff	Dose	Maximal dose	Onset of action	Maximal effect	Duration of action
SABA	Salbutamol	Inhalation	pMDI: 100 μg	200 μg every 4–6 hours	1600 μg/day	40–50 s	15–20 min	3–6 hours
	Terbutalin	Inhalation	TH: 500 μg	500 μg every 6 hours	6 mg/day	40–50 s	15–30 min	4–6 hours
LABA	Salmeterol	Inhalation	pMDI: 25 μg AH: 50 μg	50 μg every 12 hours	200 μg/day	20 min	3–4 hours	12 hours
	Formoterol	Inhalation	pMDI: 12 μg TH: 9 μg AL: 12 μg	9 or 12 μg every 12 hours	48 μg/day	1–3 min	2 hours	12 hours
	Indacaterol	Inhalation	BH: 150 μg BH: 300 μg	150 μg every 24 hours	300 μg/day	1–3 min	2 hours	24 hours
SAMA	Ipratropium bromide	Inhalation	pMDI: 20 μg	20–40 μg every 6–8 hours	320 μg/day	15 min	30–60 min	4–8 hours
LAMA	Tiotropium bromide	Inhalation	HA: 18 μg	18 μg every 24 hours	18 μg/day	30 min	3 hours	24 hours
			RM: 2.5 μg	5 μg every 24 hours	5 μg/day			
	Aclidinium bromide[c]	Inhalation	GE: 322 μg	322 μg every 12 hours	644 μg/day	15–30 min	2 hours	12 hours
	Glycopyrronium bromide[d]	Inhalation	BH: 44 μg	44 μg every 24 hours	44 μg/day	5 min	2 hours	24 hours
FDC	Indacaterol/ glycopyrronium	Inhalation	BH: 110/50 μg	110/50 μg every 24 hours	110/50 μg/day	1–3 min	2 hours	24 hours
	Vilanterol/ umeclidinium	Inhalation	EL: 25/62.5 μg	25/62.5 μg every 24 hours	25/62.5 μg/day	5 min	2 hours	24 hours
MX	Theophylline	Per os	–	5–6 mg/kg (l.d.) 2–7 mg/kg/12 hours (m.d.)	2–7 mg/kg/12 hours	3 hours	6 hours	12 hours

[a] Abbreviations: AH, Accuhaler®; AL, Aerolizer®; BH, Breezhaler®; CI, capsules for inhalation; GE, Genuair®; HA, Handihaler®; l.d., loading dose; m.d., maintenance dose; MX, methylxanthines; pMDI, pressurized metered dose inhaler; RM, Respimat®; SABA, short-acting beta$_2$-agonists; SAMA, short-acting muscarinic receptor antagonists; TH, Turbuhaler®.
[b] AH, AL, BH, HA, GE, TH are DPIs.
[c] The delivered dose, that is the amount of drug that leaves the inhaler, equivalent to aclidinium is indicated.
[d] The delivered dose, that is the amount of drug that leaves the inhaler, equivalent to glycopyrronium is indicated.

Bacterial, viral, eosinophilic, and pauci-inflammatory phenotypes of COPD exacerbations have been identified. These phenotypes are stable and related to the clinical phenotype in stable COPD [35,36]. For example, individuals with eosinophilic exacerbations usually have increased concentrations of peripheral eosinophils, even in stable state [35], and their exacerbations respond to systemic corticosteroids, in contrast to noneosinophilic exacerbations, which might have a poorer evolution with systemic corticosteroids compared with placebo [37]. It is tempting to associate infective exacerbations with the exacerbator with chronic bronchitis phenotype, eosinophilic exacerbations with the ACOS phenotype, and pauci-inflammatory exacerbations with the exacerbator with an emphysema phenotype, but confirmatory studies are needed.

Continuous or intermittent long-term treatment with antibiotics reduces COPD exacerbation frequency and increases the time to the next exacerbation [30,38], although the mechanism(s) of these effects is unclear. The benefit of long-term antibiotic treatment could be the result of eradication of colonizing bacteria and/or reduction in chronic airway inflammation, although evidence supporting this hypothesis is limited. Although macrolides have not only antibacterial, but also anti-inflammatory, immunomodulatory, and antiviral effects, in addition to a possible effect against biofilm formation, it is not known which action(s) is responsible for their efficacy when used for the long-term treatment of respiratory conditions.

Prevention of exacerbations in patients with severe disease is one of the unmet needs in COPD pharmacological treatment. Therefore, additional use of long-term oral antibiotics has been advocated in these patients. Over the past decade, six studies have reported the use of continuous long-term antibiotic treatment in patients with COPD [5,38–42] and one has reported the use of intermittent and/or pulsed treatment [30]. In the first open-label, 12-month study, erythromycin was effective in preventing COPD exacerbations [38]. The percentage of patients with COPD experiencing one or more exacerbations during the treatment period was lower in the erythromycin (11%) than in the control group (56%), with higher hospital admission rate resulting from exacerbations in the control group ($P = 0.0007$). In another study, erythromycin reduced COPD exacerbations and the median time to exacerbation over a 12-month follow-up with no differences in lung function or inflammatory markers [39]. However, other studies showed reduction in inflammatory markers and neutrophil counts following 6-month treatment with azithromycin [41] and erythromycin [42]. In a large pivotal study, reporting the use of 12-month treatment with daily azithromycin in the prevention of COPD exacerbations, the addition of azithromycin to standard therapy was associated with a 27% decrease in exacerbation rate and an increase in the median time to exacerbation (266 days versus 174 days, respectively; $P < 0.001$) [5]. In another 12-month retrospective study, azithromycin reduced exacerbations, hospitalizations, and length of hospital stay [40].

Please cite this article in press as: Montuschi, P. et al. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.08.004

BOX 2

Pharmacological modulation of airway smooth muscle cell and mechanism of action of bronchodilators.

Beta$_2$-adrenergic, muscarinic M_2, and muscarinic M_3 receptors are expressed on airway smooth muscle cell plasma membranes (Fig. 2). Binding of endogenous agonists (e.g. catecholamines), short-acting beta$_2$-agonists (SABA), or long-acting beta$_2$-agonists (LABA) to the beta$_2$-adrenergic receptor causes a conformational receptor change with G stimulatory protein (G_s) activation and subsequent enhanced adenylyl cyclase (AC) activity, which catalyzes the production of cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). Increased intracellular cAMP concentrations activates protein kinase A (PKA), triggering a cascade of intracellular events, including myosin light chain kinase inhibition, which ultimately leads to airway smooth muscle relaxation. Acetylcholine (Ach) released by parasympathetic vagal nerve endings causes airway smooth muscle contraction by activating postsynaptic muscarinic M_3 receptors. Agonist/receptor complex activates a G_q protein that, in turn, enhances phospholipase(s) C (PLC) β activity. This enzyme catalyzes the production of the second messengers inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) from the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP2). DAG activates protein kinase C (PKC), whereas IP3, by interacting with specific receptors on the endoplasmic reticulum (ER), mobilizes calcium ions (Ca^{2+}) from intracellular stores into the cytoplasm. Both events ultimately facilitate actin–myosin interaction with consequent airway smooth muscle contraction. Ach released from the vagal nerve endings can also activate presynaptic and postsynaptic M_2 muscarinic receptors. Presynaptic M_2 receptors are inhibitory autoreceptors and their activation leads to a reduction in Ach release from the nerve ending. Activation of postsynaptic M_2 muscarinic receptors, through activation of a G inhibitory protein (G_i), reduces beta$_2$ receptor-induced stimulation of AC activity. Short-acting muscarinic receptor antagonists (SAMA) and long-acting muscarinic receptor antagonists (LAMA) cause bronchodilation principally by blocking post-synaptic M_3 muscarinic receptors. More-selective inhaled muscarinic M_3 receptor antagonists (e.g. aclidinium bromide and glycopyrronium bromide) might avoid an increase in Ach released because of presynaptic M_2 blockade, but the lack of postsynaptic M_2 antagonism might increase the M_2-mediated inhibitory effect on beta$_2$-induced bronchodilatation. However, the implications of M_2 receptor modulation for the bronchodilatating effect in patients with COPD is largely unknown because data on the functional role of M_2 receptors mainly derive from *in vitro* and *in vivo* animal studies. In addition to bronchodilatating effect, inhaled muscarinic receptor antagonists reduce airway obstruction in patients with COPD by blocking postsynaptic M_3 receptors on airway submucosal mucous gland cells.

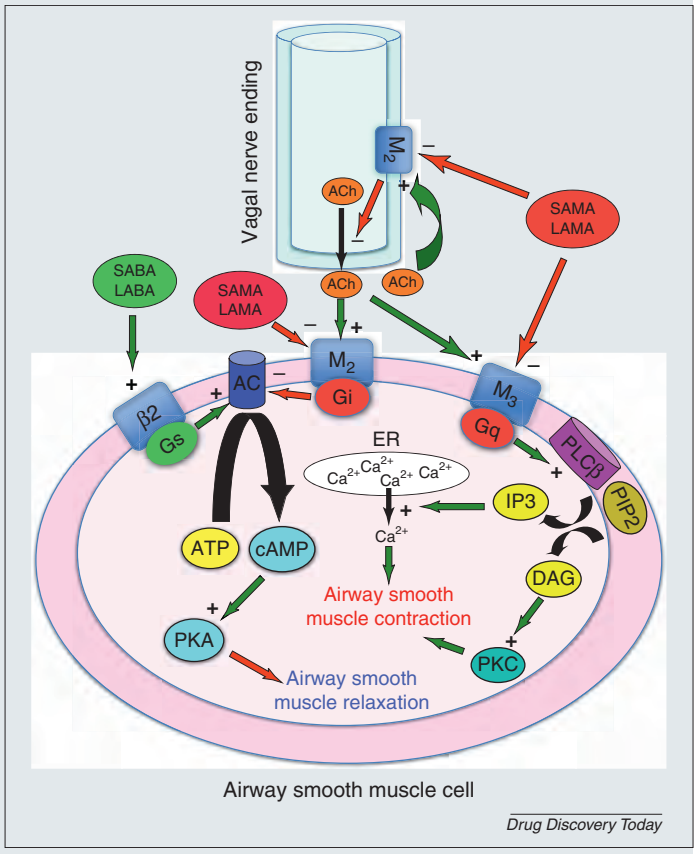

FIGURE 2

Pharmacological modulation of airway smooth muscle cell and mechanism of action of bronchodilators. Activating or facilitating effects are shown by green arrows; inhibitory or antagonistic effects are shown by red arrows. For definitions of abbreviations, see box and main text.

The risk of increasing bacterial resistance with long-term use of macrolides is a concern. In view of the large patient population affected by COPD, widespread use of macrolides, particularly azithromycin, has the potential to influence substantially antimicrobial resistance rates of a range of respiratory microorganisms [43]. In one study, the incidence of resistance to macrolides in respiratory pathogens isolated from nasopharyngeal swabs was significantly increased in the group of patients receiving azithromycin compared with the placebo group [5].

Intermittent, pulsed fluoroquinolone antibiotic therapy in patients with COPD has been reported [30]. In this study, moxifloxacin, given daily for 5 days with treatment repeated every 8 weeks for a total of six courses, reduced the odds of an exacerbation by 25% in the primary population for efficacy analysis (per protocol population as prespecified in the protocol) in patients with moderate-to-severe COPD, whereas in a post hoc analysis, this reduction was 45% in patients with purulent or mucopurulent sputum at baseline [30]. No relevant bacterial resistance was reported with intermittent moxifloxacin treatment [30]. However, it cannot be ruled out that more prolonged courses of intermittent treatment with this or other antibiotics might result in increased resistance. Therefore, careful stratification of patients is required before this therapy can be recommended.

Long-term azithromycin treatment caused changes in nasal bacteria flora, increasing the prevalence of macrolide-resistant bacteria [5]. Possible hearing loss associated with long-term use of macrolides [5] as well as concerns of increased antibiotic resistance, indicate that, until further well-controlled studies are conducted, such treatment should be limited to patients with severe COPD who experience frequent exacerbations requiring multiple antibiotic treatments despite optimal bronchodilator and anti-inflammatory therapy [27].

Please cite this article in press as: Montuschi, P. et al. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.08.004

In general, guidelines do not recommend long-term antibiotic treatment for the prevention of COPD exacerbations (http://www.goldcopd.com). However, evidence for efficacy of macrolides and, to a lesser extent, quinolones has been accumulating over the past few years. More recent guidelines have included, for the first time, a recommendation related to the use of long-term antibiotic treatment in a specific subgroup of patients with severe COPD, namely those with chronic bronchitis and frequent exacerbations [27]. However, this treatment must be monitored closely for the possible development of adverse effects and/or changes in bacterial resistance patterns.

Pharmacological treatment of ACOS

Epidemiological studies of COPD incidence show that young asthmatic smokers developing not fully reversible airflow obstruction (i.e. COPD by definition) have a disease with different characteristics compared with those with persistent airflow obstruction but no history of asthma [44]. In the first case, allergic rhinitis, airway hyper-responsiveness, and wheezing, together with elevated serum immunoglobulin (Ig) E concentrations are significantly more frequent, indicating that this is an overlap phenotype between asthma and COPD [44]. ACOS has been defined as the coexistence of increased variability of airflow in a patient with incompletely reversible airway obstruction [45,46] or as the diagnosis of COPD in a patient with a history of previously diagnosed asthma before the age of 40 [47]. More specifically, a mixed COPD–asthma phenotype, as defined principally on the basis of clinical-functional criteria (history of asthma and a very positive reversibility test to bronchodilators) and cellular criteria (sputum eosinophilia), has been identified [48]. Patients with ACOS share characteristics of both diseases and represent a challenge in differential diagnosis, particularly in primary care [49]. The prevalence of this mixed phenotype is unknown, but there are different estimates of its importance in the context of COPD. The COPD Gene Cohort found ACOS in 13% of their sample [47]. Soriano *et al.* estimated that approximately 23% of patients with COPD aged 50–59 years could have a mixed phenotype, with this percentage increasing with age [9]. The relevance of this phenotype, already described in the Canadian [50] and Japanese [51] guidelines, is its enhanced response to corticosteroids [50–54]. Although the role of bronchodilators in both phenotypes is defined, whether patients with a mixed COPD–asthma phenotype have a greater response to ICS as an add-on treatment to double bronchodilator than patients with COPD and a non-mixed phenotype is currently unknown. A recent study showed that 25% of patients with COPD are overtreated with ICS with negative consequences in terms of adverse effects, including increased risk of pneumonia, and costs associated with overuse [55].

There are no studies aimed at establishing the efficacy of ICS treatment in the mixed phenotype or investigating ICS effects in mixed compared with the nonmixed COPD phenotype. Some studies have investigated CS effects on symptoms and lung function in a cohort of patients with COPD that was then divided in subgroups based on an ACOS characteristic (e.g. sputum eosinophilia) [52–54].

In a randomized, double-blind, placebo-controlled, crossover trial in 67 patients with COPD who were being treated with bronchodilators (29 with sputum eosinophils > 3%; eosinophilic phenotype), treatment with oral prednisolone at a daily dose of 30 mg for 2 weeks produced a six-times decrease in the mean sputum eosinophil count, which was not observed with placebo [54]. Overall, there were no treatment-associated changes in lung function or symptom scores. However, after stratifying into tertiles by baseline eosinophil count, post-bronchodilator FEV_1 (mean difference 0.19 L, 95% CI 0.06–0.32) and chronic respiratory questionnaire (CRQ) scores (mean difference 0.62, 95% CI 0.31–0.93) improved progressively following prednisolone from the lowest to the highest eosinophilic tertile, compared with placebo [54]. Likewise, in a similar study by the same group in 60 patients with COPD, a significant improvement in post-bronchodilator FEV_1 (mean difference 0.11 L, 95% CI 0.03–0.19) with inhaled mometasone furoate (given at a dose of 800 μg daily for 4 weeks) compared with placebo was only observed in patients with COPD and sputum eosinophil counts > 3.9% ($n = 20$) [52]. However, this effect was not associated with a reduction in sputum eosinophils or improvement in CRQ, possibly because of a dose of mometasone used in this study insufficient for achieving optimal effects [52].

A sequential, single-blind, crossover trial with inhaled budesonide at a dose of 800 μg twice daily for 4 weeks showed a clinically relevant improvement in dyspnea and a small, but statistically significant, improvement in FEV_1 compared with placebo [53]. These effects were observed in the 15 patients with COPD and sputum eosinophilia, but not in the 25 patients with COPD but without sputum eosinophilia, and were paralleled by a normalization of sputum eosinophil counts in patients with COPD and an eosinophilic phenotype [53]. Another study showed that a management strategy that aimed to minimize eosinophilic airway inflammation, as well as symptoms, was associated with a reduction in severe exacerbations of COPD [56]. Although relatively small, these studies suggest that short-term treatment with ICS in patients with COPD and sputum eosinophilia, which is a component of ACOS, might improve lung function and symptoms by reducing airway inflammation. However, larger prospective controlled studies are required to establish the long-term effects of maintenance treatment with ICS in patients with ACOS in terms of reduction of exacerbations and lung function decline.

The only available pharmacological study in patients with ACOS was performed with tiotropium [57], but no comparative studies including patients with non-ACOS have been performed. In 472 patients included in a 12-week randomized, double-blind, placebo-controlled parallel group study, inhaled tiotropium at a daily dose of 18 μg improved the primary endpoint FEV_1 area under the curve (AUC) from 0 to 6 hours (186 ± 24 ml difference, $P < 0.001$) and morning pre-dose FEV_1 (98 ± 23 ml difference, $P < 0.001$) compared with baseline values [57]. Pre-dose forced vital capacity (FVC) and FVC AUC 0–6 hours also improved [57]. Large prospective controlled powered studies are required to determine the efficacy of pharmacological treatment, particularly ICS, in patients with ACOS compared with patients with non-ACOS.

Identification of subphenotypes of patients with COPD who are most likely to respond to ICS (e.g. COPD–asthma mixed phenotype), could help define the role of these drugs in COPD and pave the way for implementing personalized pharmacological

Please cite this article in press as: Montuschi, P. et al. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.08.004

TABLE 2

Pharmacological treatment of COPD based on phenotypes and disease severity (GOLD stage I–IV)[a,b]

Phenotype	Disease severity			
	I	II	III	IV
Non-exacerbator	LAMA or LABA SABA or SAMA[c]	LAMA or LABA LAMA + LABA	LAMA + LABA	LAMA + LABA + theophylline
ACOS	LABA + ICS	LABA + ICS	LAMA + LABA + ICS	LAMA + LABA + ICS (consider adding theophylline or PDE_4 inhibitors if expectoration and exacerbations are present)
Exacerbator with emphysema	LAMA or LABA	LABA or LAMA + ICS LABA + ICS LAMA + LABA LAMA or LABA	LAMA + LABA + ICS	LAMA + LABA + ICS (consider adding theophylline)
Exacerbator with chronic bronchitis	LAMA or LABA	LAMA or LABA + ICS or PDE_4 inhibitors LABA + ICS LAMA + LABA LAMA or LABA LAMA or LABA + PDE_4 inhibitors	LAMA + LABA + ICS or PDE_4 inhibitors LAMA or LABA + ICS + PDE_4 inhibitors (consider adding mucolytics)	LAMA + LABA + ICS or PDE_4 inhibitors LAMA + LABA + ICS + PDE_4 inhibitors (consider adding mucoltics; theophylline; and/or antibiotics)

[a] Based on Ref. [27].

[b] Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta$_2$-agonists; LAMA, long-acting muscarinic receptor antagonists; PDE_4, phosphodiesterase 4; SABA, short-acting beta$_2$-agonists; SAMA, short-acting muscarinic receptor antagonists.

[c] In case of intermittent symptoms.

strategies. Analysis of sputum inflammatory cells could translate into an effective tool for predicting ICS response in patients with COPD. Given that many patients with COPD are prescribed long-term high-dose treatment, a more rational ICS use could reduce healthcare expenses resulting from adverse effects, including iatrogenic fractures and increased risk for pneumonia, and the high cost of these drugs.

Concluding remarks

Patients with COPD are characterized by a large clinical, functional, radiological, cellular, and molecular phenotype variability that, in turn, is reflected by an equally large variability in disease progression and response to pharmacological treatment. Current classification of COPD severity, principally based on symptoms, pulmonary function testing, and exacerbation rate as proposed by GOLD guidelines (http://www.goldcopd.com), has therapeutic implications because patients with COPD who have very different features and, possibly, a very different response to pharmacological treatment, are treated in the same way. The treatment approach based on phenotypes represents a significant change in the management of COPD, from treatment focused on the severity of the airflow limitation to a more personalized approach directed by clinical, functional, morphological, and, ideally, molecular features.

Four different phenotypes characterized by the combination of the classical types of emphysema and chronic bronchitis with infrequent exacerbator, frequent exacerbator, and ACOS, have been proposed: (i) infrequent exacerbator, with either chronic bronchitis or emphysema; (ii) ACOS; (iii) frequent exacerbator with predominant emphysema; and (iv) frequent exacerbator with predominant chronic bronchitis [27]. These phenotypes identify patients with different response to pharmacological treatment [60] and enable a more personalized pharmacotherapeutic approach, which is modulated according to COPD severity (Table 2).

Large pharmacological clinical trials have included unselected populations of patients with COPD and analyzed the results as comparisons of mean values between treatment groups without considering the possibility of the existence of different populations of responders and nonresponders to a given drug [58]. New studies need to incorporate subgroup analysis of pharmacological response by clinical characteristics [4,5] or even be restricted to particular phenotypes to investigate the response to therapy in a group of patients with common characteristics [57]. The results of these trials will help to personalize treatment for this complex disease. Molecular phenotyping of COPD through 'omics' platforms is likely to lead to an even more personalized pharmacological treatment of individual patients with COPD.

In the meantime, we can use the classical phenotypes described here to identify subgroups of patients that are likely to respond to different pharmacological treatments. Including these rapidly recognizable clinical phenotypes in management guidelines might help clinicians to select the most effective pharmacological treatments for their patients. Nonetheless, this approach has to be validated in future clinical studies.

Acknowledgements

This work was supported by the Catholic University of the Sacred Heart, Fondi di Ateneo 2012–2014.

Please cite this article in press as: Montuschi, P. et al. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.08.004

References

1 Anonymous (1995) American Thoracic Society Statement. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 152, S77–S120

2 Pauwels, R.A. *et al.* (2001) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 163, 1256–1276

3 Yusen, R.D. (2013) Evolution of the GOLD documents for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Controversies and questions. *Am. J. Respir. Crit. Care Med.* 188, 4–5

4 Rennard, S.I. *et al.* (2011) Reduction of exacerbations by the PDE_4 inhibitor roflumilast – the importance of defining different subsets of patients with COPD. *Respir. Res.* 12, e18

5 Albert, R.K. *et al.* (2011) Azithromycin for prevention of exacerbations of COPD. *N. Engl. J Med.* 365, 689–698

6 Miravitlles, M. (2011) Arguments in favor of inhaled corticosteroids in COPD by phenotype instead of by severity. *Arch. Bronconeumol.* 47 271–271

7 Anderson, D. and MacNee, W. (2009) Targeted treatment in COPD: a multi-system approach for a multi-system disease. *Int. J. Chron. Obst. Pulm. Dis.* 4, 321–335

8 Han, M.K. *et al.* (2010) Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am. J. Respir. Crit. Care Med.* 182, 598–604

9 Soriano, J.B. *et al.* (2003) The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. *Chest* 124, 474–481

10 Burrows, B. *et al.* (1966) The emphysematous and bronchial types of chronic airflow obstruction. *Lancet* 1, 830–835

11 Montuschi, P. *et al.* (2013) Inhaled muscarinic acetylcholine receptor antagonists for treatment of COPD. *Curr. Med. Chem.* 20, 1464–1476

12 Fuso, L. *et al.* (2013) Long-acting beta-agonists and their association with inhaled corticosteroids in COPD. *Curr. Med. Chem.* 20, 1477–1495

13 Kerwin, E. *et al.* (2012) Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. *Eur. Respir. J.* 40, 1106–1114

14 Gelb, A.F. *et al.* (2013) Long-term safety and efficacy of twice-daily aclidinium bromide in patients with COPD. *Respir. Med.* 107, 1957–1965

15 Beier, J. *et al.* (2013) Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb study. *COPD* 10, 511–522

16 Brown, S.M. *et al.* (2013) A role for M_2 and M_3 muscarinic receptors in the contraction of rat and human small airways. *Eur. J. Pharmacol.* 702, 109–115

17 Bateman, E.D. *et al.* (2013) Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur. Respir. J.* 42, 1484–1494

18 Vogelmeier, C.F. *et al.* (2013) Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir. Med.* 1, 51–60

19 Frampton, J.E. (2014) QVA149 (indacaterol/glycopyrronium fixed-dose combination): a review of its use in patients with chronic obstructive pulmonary disease. *Drugs* 74, 465–488

20 Scott, L.J. and Hair, P. (2014) Umeclidinium/vilanterol: first global approval. *Drugs* 74, 389–395

21 Feldman, G.J. and Edin, A. (2013) The combination of umeclidinium bromide and vilanterol in the management of chronic obstructive pulmonary disease: current evidence and future prospects. *Ther. Adv. Respir. Dis.* 7, 311–319

22 Bateman, E.D. *et al.* (2013) Pharmacodynamics of GSK961081, a bi-functional molecule, in patients with COPD. *Pulm. Pharmacol. Ther.* 26, 581–587

23 Hurst, J.R. *et al.* (2010) Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N. Engl. J. Med.* 363, 1128–1138

24 Soler Cataluña, J.J. *et al.* (2011) The frequent exacerbator. A new phenotype in COPD? *Hot Topics Respir. Med.* 6, 7–12

25 Quint, J.K. *et al.* (2011) Predictive accuracy of patient-reported exacerbation frequency in COPD. *Eur. Respir. J.* 37, 501–507

26 Soler-Cataluña, J.J. *et al.* (2005) Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 60, 925–931

27 Miravitlles, M. *et al.* (2012) Spanish COPD guidelines (GesEPOC). Pharmacological treatment of stable COPD. *Arch. Bronconeumol.* 48, 247–257

28 Montes de Oca, M. *et al.* (2012) Chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. *Eur. Respir. J.* 40, 28–36

29 Kim, V. *et al.* (2011) The chronic bronchitic phenotype of COPD. An analysis of the COPD Gene study. *Chest* 140, 626–633

30 Sethi, S. *et al.* (2010) Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Respir. Res.* 11, e10

31 Poole, P.J. and Black, P.N. (2006) Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* 3, eCD001287

32 Zheng, J.P. *et al.* (2008) Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomized placebo-controlled study. *Lancet* 371, 2013–2018

33 Decramer, M. *et al.* (2005) Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomized placebo-controlled trial. *Lancet* 365, 1552–1560

34 Han, M.K. *et al.* (2011) Chronic obstructive pulmonary disease exacerbations in the COPD Gene Study: associated radiologic phenotypes. *Radiology* 261, 274–282

35 Bafadhel, M. *et al.* (2011) Acute exacerbations of chronic obstructive pulmonary disease. Identification of biologic clusters and their biomarkers. *Am. J. Respir. Crit. Care Med.* 184, 662–671

36 Hurst, J. (2011) Exacerbation phenotyping in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 184, 625–626

37 Bafadhel, M. *et al.* (2012) Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease. A randomized placebo-controlled trial. *Am. J. Respir. Crit. Care Med.* 186, 48–55

38 Suzuki, T. *et al.* (2001) Erythromycin and common cold in COPD. *Chest* 120, 730–733

39 Seemungal, T.A. *et al.* (2008) Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am. J. Respir. Crit. Care Med.* 178, 1139–1147

40 Pomares, X. *et al.* (2011) Long-term azithromycin therapy in patients with severe COPD and repeated exacerbations. *Int. J. Chron. Obstruct. Pulmon. Dis.* 6, 449–456

41 Blasi, F. *et al.* (2010) Long-term azithromycin use in patients with chronic obstructive pulmonary disease and tracheostomy. *Pulmon. Phamacol. Ther.* 23, 200–207

42 He, Z-Y. *et al.* (2010) Effect of 6 months of erythromycin treatment on inflammatory cells in induced sputum and exacerbations in chronic obstructive pulmonary disease. *Respiration* 80, 445–452

43 Serisier, D.J. (2013) Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respir. Med.* 1, 262–274

44 De Marco, R. *et al.* (2007) Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *Am. J. Respir. Crit. Care Med.* 175, 32–39

45 Gibson, P.G. and Simpson, J.L. (2009) The overlap syndrome of asthma and COPD: what are its features and how important is it? *Thorax* 64, 728–735

46 Miravitlles, M. (2011) The overlap syndrome between asthma and COPD: implications for management. *Hot Topics Respir. Med.* 16, 15–20

47 Hardin, M. *et al.* (2011) The clinical features of the overlap between COPD and asthma. *Respir. Res.* 12, e127

48 Soler Cataluña, J.J. *et al.* (2012) Consensus document on the overlap phenotype COPD–asthma in COPD. *Arch. Bronconeumol.* 48, 331–337

49 Miravitlles, M. *et al.* (2012) Difficulties in differential diagnosis of COPD and asthma in primary care. *Br. J. Gen. Pract.* 62, e68–e75

50 O'Donnell, D.E. *et al.* (2007) Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2007 update. *Can. Respir. J.* 14 (Suppl. B), 5B–32B

51 Nagai, A. *et al.* (2009) *Guidelines for the Diagnosis and Treatment of COPD* (edn 3), The Japanese Respiratory Society

52 Brightling, C.E. *et al.* (2005) Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. *Thorax* 60, 193–198

53 Leigh, R. *et al.* (2006) Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. *Eur. Respir. J.* 27, 964–971

54 Brightling, C.E. *et al.* (2000) Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 356, 1480–1485

55 White, P. *et al.* (2013) Overtreatment of COPD with inhaled corticosteroids: implications for safety and costs: cross–sectional observational study. *PLoS ONE* 8, e75221

56 Siva, R. *et al.* (2007) Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. *Eur. Respir. J.* 29, 906–913

57 Magnussen, H. *et al.* (2008) Improvements with tiotropium in COPD patients with concomitant asthma. *Respir. Med.* 102, 50–56

58 Calverley, P.M.A. *et al.* (2007) Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N. Engl. J. Med.* 356, 775–778

59 Gibb, A. and Yang, L.P. (2013) Olodaterol: first global approval. *Drugs* 73, 1841–1846

60 Miravitlles, M. *et al.* (2013) Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. *Eur. Respir. J.* 41, 1252–1256

Please cite this article in press as: Montuschi, P. et al. Pharmacological treatment of chronic obstructive pulmonary disease: from evidence-based medicine to phenotyping, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2014.08.004