Systemic Medications in Chronic Obstructive Pulmonary Disease
Use and Outcomes

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KEYWORDS

• COPD • Theophylline • Phosphodiesterase inhibitors • Oral corticosteroids • Macrolides • Mucoactive agents • Alpha1-antitrypsin • Morphine

KEY POINTS

- Systemic treatments of chronic obstructive pulmonary disease (COPD) are not first-line therapeutic options.
- The benefit/risk ratio of oral beta2-adrenergic agonists and xanthines is not favorable.
- Azithromycin, phosphodiesterase 4 inhibitors, and mucomodifiers can contribute to exacerbation prevention in patients on inhaled therapy.
- The long-term use of systemic corticosteroids in COPD should be strongly discouraged.
- Several biologics are currently in development for COPD therapy and may prove useful in particular subpopulations identified through the use of specific biomarkers.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is now defined by the coexistence of chronic respiratory symptoms and permanent (ie, not fully reversible) airflow limitation, caused by airways and parenchymal disease.[1] The development of airflow obstruction and emphysema is the consequence of a close interplay between inflammation, innate and adaptive immune reactions, protease-antiprotease imbalance, and oxidative stress, leading to airway wall and parenchymal remodeling and mucus hypersecretion.[2–6] Associated phenomena include chronic infection/colonization/microbiota modifications, autoimmunity, senescence, and systemic inflammation.[7,8]

Although some decades ago systemic treatments (ie, theophylline and oral corticosteroids for very severe cases) represented the main therapeutic approach for patients with COPD, inhaled medications are now the cornerstone of COPD treatment.[1] They have the obvious advantage of delivering high local concentrations of effective medication, while minimizing systemic absorption and side effects. However, because of these properties, they do not exert any significant effect on the systemic components of the disease, which have been repeatedly emphasized in the last 15 years.[9] The comorbidities and systemic features frequently seen in patients with COPD include muscle deconditioning, malnutrition, osteoporosis, psychological distress (anxiety-depression), cognitive impairment, metabolic and cardiovascular diseases, anemia, and lung cancer.[10–12] In the mid 2000s there was great enthusiasm around the concept of systemic inflammation as a common trigger for all of these conditions, with many studies showing increases in several systemic inflammatory biomarkers.

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However, the exact relation between COPD and underlying pathophysiologic mechanisms remained uncertain. At present, decreased physical activity (also associated with systemic inflammation) is viewed as a major common contributor to most systemic aspects of COPD.[13] The increased frequency of cardiovascular events and treatments in patients with COPD also led to some interest in the possible interaction between inflammatory bursts and/or increases in lung hyperinflation with COPD outcomes, and this is the most plausible mechanism helping explain the increased risk of major cardiovascular events following acute exacerbations.[10]

In addition to their lack of effects on the systemic component of COPD, inhaled treatments may not be sufficiently effective to deliver pharmaceutical agents to the small airways, where most of the disease processes outlined earlier reside.[14]

This article reviews the effects of systemic agents with a main focus on clinical outcomes and long-term maintenance use. Pharmaceutical families of interest include oral beta2 agonists, theophylline, phosphodiesterase (PDE) inhibitors, macrolides with antiinflammatory properties and other antibiotics, mucoactive agents, corticosteroids, antileukotrienes, cardiovascular drugs, and biologics.

ORAL BETA2-ADRENERGIC AGONISTS

The benefit/risk ratio of oral beta2 agonists is much less favorable than that of their inhaled counterparts, because high systemic levels are required to achieve sufficient local concentrations leading to bronchodilation. At therapeutic doses, side effects (tremor, tachycardia) are more frequent and intense, whereas bronchodilation is similar[15] or less pronounced[16] than the inhaled presentation. In addition, these agents have been assessed only in small short-term studies with no patient-reported outcome end points. As a consequence, they are not recommended for COPD treatment except when the use of any inhaled treatment is impossible.

XANTHINES, THEOPHYLLINE

Theophylline is a xanthine structurally similar to caffeine that was initially developed for asthma in the late 1930s, at a time when COPD was not even well recognized.[17–19] Its main mechanisms of action are adenosine receptor (A1 and A2) inhibition (high potency at therapeutic concentrations) and (weak) PDE-3 and PDE-4 selective inhibition at higher and poorly tolerated concentrations.[20] Through these pathways, it exerts numerous immunomodulatory and antiinflammatory effects and has weak bronchodilator properties. Interestingly, theophylline decreases neutrophilic and eosinophilic airways inflammation, which can both be involved in patients with COPD, depending on the underlying endotype (ie, pathophysiologic profile). It also modulates lymphocytes functions.

The acute physiologic effects of theophylline include bronchodilation, lung deflation, improved gas exchanges, increased diaphragmatic function, reduced work of breathing, and improved mucociliary clearance. How these numerous demonstrable effects translate into clinical improvements is less clear, which is largely explained by the narrow therapeutic index of the drug; for instance, bronchodilation and diaphragmatic improvements need high doses to be clinically meaningful, which exposes patients to risks of serious dose/concentration-dependent side effects such as gastrointestinal (GI) perturbations (nausea, vomiting, exacerbated gastroesophageal reflux), tremor, sleep disturbance, headache, seizures, arrhythmias, and heart failure. In addition, many factors can interact with theophylline serum concentrations, including diseases that are frequently seen in patients with COPD, such as heart failure, liver disease, and smoking. In addition, theophylline serum concentrations vary depending on its interaction with several concomitant drugs (including antibiotics used in COPD exacerbations), the elimination of which is modulated by the cytochrome P (CYP) 1A2 or CYP3A4 coenzymatic activity (**Table 1**). Thus, using theophylline often requires monitoring its blood concentrations, further influencing its ease of use. As a consequence, and particularly in acute situations, the acute use of theophylline has been widely abandoned because of the need for high serum concentrations to achieve clinically meaningful bronchodilation or diaphragmatic improvement, and the associated risk of significant toxicity.

Regarding long-term use, there has been some interest in one particular property of theophylline: restoration of histone-deacetylase 2 (HDAC2) activity.[21] HDAC2 is an important cofactor of corticosteroids effects because it interacts with the corticosteroid-glucocorticoid receptor, contributing to chromatin condensation and thereby inhibiting the transcription and subsequent expression of proinflammatory genes (transrepression).[22] In smokers, and even more in patients with COPD, the oxidative stress impairs HDAC2 function, representing 1 of the numerous mechanisms of corticosteroid resistance.[23] Thus, conceptually theophylline could restore the effects of corticosteroids, which are reduced in smokers and in COPD. This mode of action could be of

Table 1
Main modulators of theophylline's pharmacokinetics

Effect	Increased Bioavailability	Reduced Bioavailability
Disease/condition	Viral infections Congestive heart failure Liver diseases	—
Age	—	Children<16 y
Toxic agents	—	Cigarette and marijuana smoking
Medications (through CYP1A2 and CYP3A4 modulation)	Erythromycin, clarithromycin (not azithromycin), ciprofloxacin (not ofloxacin), cimetidine (not ranitidine) allopurinol, serotonin uptake inhibitors, flu vaccination	Phenytoin, phenobarbitone, rifampicin

Data from Refs.[18,20]

particular interest because it occurs at serum concentrations that are approximately half the threshold of toxicity. Following encouraging results from in vitro experiments on HDAC2 activity and corticosteroid cellular effects, this hypothesis has been clinically tested in 2 randomized controlled trials, with disappointing results regarding all variables of clinical interest (ie, lung function, exacerbations, symptoms, and quality of life).[24,25]

As a consequence, the use of theophylline has been largely abandoned as part of long-term maintenance therapy. However, in some areas of the world, Cost-issues are such that theophylline is one of a few affordable options, together with a few low-cost (but still very effective) inhaled drugs such as salbutamol and beclomethasone.

The theophylline/xanthines family includes not only theophylline but also its derivatives aminophylline (the oldest one), bamiphylline, and doxophylline. The main potential difference between these agents is the efficacy/safety profile, which might be better for doxophylline according to a recent network meta-analysis.[19] How this translates into clinical superiority at the individual patient level is not fully clear.

PHOSPHODIESTERASE 4 INHIBITORS

PDE-4 inhibitors are often wrongly considered as modern theophyllines. This concept is not valid because most of the clinical effect of theophylline observed at nontoxic doses are linked to adenosine receptor antagonism, whereas effective PDE inhibition occurs only at toxic or close-to-toxic doses. Real selective PDE inhibitors commercially available at present are limited to one agent, roflumilast, which is not authorized or reimbursed in all countries. Another agent, cilomilast, was provisionally approved in the early 2000s but its development has been abandoned because of concerns about its efficacy/safety profile.[26]

There are many subtypes of PDE-4 (A, B, C, and D) and more than 25 isoforms, many of which are expressed in various inflammatory and resident cell types in the airways.[17,27,28] The potential beneficial effects of PDE-4 inhibition are numerous because PDE-4 is involved in cyclic AMP (cAMP) degradation. Thus, PDE-4 inhibition increases cellular levels of cAMP, which acts as an antiinflammatory second messenger decreasing the release of inflammatory mediators and the expression of proinflammatory surface receptors (eg, adhesion molecules) by neutrophils and other cell types, including macrophages, eosinophils, and T lymphocytes. Roflumilast (through its active metabolite roflumilast N-oxide) reduces the recruitment of inflammatory cells in the airways. cAMP is also involved in smooth muscle relaxation, but the bronchodilator effect of roflumilast at therapeutic concentrations is limited. In animal models, roflumilast prevents cigarette smoke–induced lung inflammation and emphysema.[18]

In humans, following the first studies and their subgroup analyses, roflumilast has been shown to reduce the risk of exacerbations in patients with COPD and frequent exacerbations (or previous hospitalization), severe airflow obstruction (Global initiative on Obstructive Lung Disease [GOLD] 3–4, postbronchodilator forced expiratory volume in 1 second [FEV_1] <50% predicted), symptoms of chronic bronchitis, and receiving bronchodilator therapy.[29] This beneficial effect occurs even in patients receiving concomitant treatment with inhaled long-acting bronchodilators and corticosteroids and is accompanied by an improvement in lung function, although the

increase in FEV_1 (mean, 51 mL) does not reach the classic (but debatable for therapies administered on top of active medications) threshold for clinical significance (100 mL).[30] These effects have been confirmed by Cochrane systematic reviews collating data from 20 studies using roflumilast in more than 17,000 participants,[29] in which small improvements in symptoms and quality of life were also noted.

Roflumilast shares GI side effects with xanthines but, in contrast with those agents, it is not associated with an increased risk of cardiovascular effects. It can induce moderate weight loss (3 kg on average), mostly related to a decrease in fat mass. GI side effects can lead to treatment interruption.

Compounds with both PDE-3 and PDE-4 inhibitory activity have been assessed in humans with no success because of lack or safety and/or unacceptable side effects. A new agent of this family administered through the inhaled route, ensifentrine, is currently being tested in clinical trials.[31] Currently available data are insufficient to draw conclusions.

MACROLIDES AND OTHER ANTIBIOTICS

The most studied macrolide for long-term maintenance therapy in COPD is azithromycin,[32,33] although earlier clinical studies were reported using erythromycin.[34] Antiinflammatory and immune-modulating properties are a feature of these macrolides.[18,35] Their first applications were the successful treatment of diffuse panbronchiolitis with erythromycin, and cystic fibrosis colonized by *Pseudomonas aeruginosa* with azithromycin. Animal models have confirmed the antiinflammatory effects of this agent, which can also prevent cigarette smoke–induced development of emphysema.[18,35] Macrolides also have the potential to augment HDAC2 expression, thereby potentially restoring corticosteroid sensitivity.

During the late 2000s, 3 studies showed the preventive effect of erythromycin on exacerbation occurrences. Subsequent trials showed a similar effect using azithromycin. Although some individual studies failed to achieve the same success, an overall positive effect was shown in a meta-analysis.[36] Studies with roxithromycin and clarithromycin did not provide convincing evidence but did not have a sufficiently robust design because they had a low sample size and were of limited duration.[35]

Considering the beneficial effect of both erythromycin and azithromycin (although they have never been directly compared), 4 main questions arise. First, selection of the best agent and the best scheme of administration. In terms of convenience of use, azithromycin is clearly the preferred drug: once versus twice or 3 times a day for erythromycin. Trials used a 250 mg/d or greater than 500 mg 3 times a week scheme,[35] although 250 mg 3 times a week is probably used more often in clinical practice as in cystic fibrosis (in which the efficacy of this protocol was shown), despite a lack of formal evaluation in COPD.

Second, the most appropriate target population. The largest study with erythromycin recruited 109 patients in a single center. There were no exacerbation-related inclusion criteria, but more than one-third of the population reported at least 3 exacerbations during the 12 months preceding inclusion, and median exacerbation frequency in the placebo group was 2, suggesting a population of frequent exacerbators.[37] The rate reduction of exacerbations in the active arm was 36% and, in addition, erythromycin reduced not only the rate but also the duration of exacerbations. Responders analysis was not performed and would have been difficult considering the limited sample size. The effect on exacerbation was not associated with effects on biomarkers of inflammation or bacterial loads in the airways, preventing any firm conclusions regarding the mechanisms of observed efficacy. Azithromycin was studied over 12 months in the largest macrolide trial ($n = 1142$).[32] Patients were on supplemental oxygen, had received systemic corticosteroids, or had been hospitalized for an exacerbation during the previous year. There was a 17% overall risk reduction in exacerbations. Responders analysis found the greatest benefit in ex-smokers, older patients, and milder GOLD stages.[38] However this analysis was post hoc, requiring further confirmation before drawing firm conclusions. The other 12-month study on azithromycin was performed in patients with a history of 3 or more exacerbations in the previous year, most of whom received triple inhaled therapy. Overall it remains difficult to define a specific target subgroup, although baseline exacerbation risk is an appropriate selection criterion.

The third question relates to risks associated with long-term macrolide therapy.[35] GI side effects (diarrhea), impairments in liver function, and a minimal increase in hearing loss have been reported. Although there is a theoretic risk of increased cardiac arrhythmias, caused by the potential increase in the corrected QT (QTc) electrocardiographic interval, this was not observed in any of the trials. However, patients with prolonged QTc interval were excluded from those trials. In practice, it may be important to consider its use primarily in

patients with normal electrocardiograms. An increase in the proportion of macrolide-resistant microorganisms in nasal swabs has been observed, although the absolute number of patients colonized by such bacteria did not change. The bacteriologic consequences of long-term macrolide use in COPD populations remains unknown. The last important question is the duration of treatment. For this question, there is no firm answer at present. Conclusive trials have lasted 6 to 12 months, and no trial of sequential administration (eg, during the winter period) has been performed.

Regarding other (nonmacrolide) antibiotics, the only sufficiently powered trial was performed with pulsed moxifloxacin (400 mg/d 5 days every 8 weeks), which produced a nonsignificant trend toward a reduction in exacerbations and is thus considered a negative trial.[39]

MUCOMODIFIERS

There are 2 main potential reasons for considering the use of mucoactive agents in COPD[40]: first, chronic mucus hypersecretion is thought to play an important role in the pathophysiology and natural course of the disease. The mucus is more abundant and viscous in many patients with COPD and is responsible for small airways obstruction, which is associated with poor prognosis in patients undergoing lung volume reduction surgery. In smokers and patients with COPDs, chronic mucus hypersecretion is also associated with several prognostic variables (FEV_1 decline and development of COPD, exacerbation and hospitalization risk, and mortality). Mucin concentrations (MUC5B, MUC5AC) seem to play a key role in the pathogenesis of chronic bronchitis.[5]

Several mucoactive agents have antioxidant properties, and oxidative stress is thought to be involved in the pathobiology of COPD, both at local (airways) and systemic levels.[6] Its consequences include inflammatory cells recruitment, protease-antiprotease imbalance, and production of proinflammatory mediators. Paradoxically, there has been no firm demonstration of an effect of most mucoactive agents on mucociliary clearance in vivo in humans. In vitro data and animal models found effects on airway wall remodeling, chemotaxis, and activation of neutrophils and monocytes/macrophages as well as decreasing bacterial adherence. In vivo during acute exacerbations, a reduction in levels of inflammatory markers and an improvement in bacterial elimination and symptoms has been found but was not accompanied by effects on hard end points such as lung function or length of stay in the hospital, questioning the clinical relevance of biological effects. Some mucoactive agents (carbocysteine, N-acetylcysteine, erdosteine, and ambroxol) have reduced the occurrence of COPD exacerbations in several trials, a finding that is supported by the results of a meta-analysis.[41] One of those trials found a reduction in exacerbation rate only in patients not taking inhaled corticosteroids (ICS), whereas the other found a reduction in the overall population, in which only a minority (<20%) of patients received ICS, suggesting that mucoactive agents may prove effective only in patients with suboptimal inhaled therapy. This point was further tested in a specifically designed large study that did not find any interaction between ICS and effects of N-acetylcysteine on exacerbations occurrence. This finding was confirmed in a more recent network meta-analysis in which a metaregression was performed to identify factors associated with treatment response.[41] Surprisingly, this analysis identified a trend toward less response in Chinese populations. This finding needs to be interpreted with caution considering the significant heterogeneity observed in the meta-analysis.

ORAL CORTICOSTEROIDS

The long-term use of oral corticosteroids is discouraged in COPD because of the well-known burden of side effects,[42] contrasting with the lack of evidence of clinically relevant beneficial effects.

Systemic dose-dependent side effects include fractures, diabetes, cataracts, hypertension, open-angle glaucoma, skin bruising, muscular weakness, cardiovascular events, and cerebrovascular events. Many of these effects can have major consequences leading to severe health status impairment. In addition, the use of oral corticosteroids has been linked to increased mortality and reduced efficacy of nutritional supplementation, a component of pulmonary rehabilitation.[43,44] The combination of COPD and oral corticosteroids also increases the risk of infections that may have particularly disastrous consequences in patients with severe lung function impairment, such as mycobacteria, *Aspergillus* spp, and various types of bacteria involved in chronic airways colonization/infection and pneumonia.

The most recent meta-analysis by the Cochrane Collaboration on oral corticosteroids for stable COPD was published in 2005.[45] Treatment lasted more than 3 weeks in only 5 studies among the 24 that were identified. Combining all studies, the mean FEV_1 improvement was 53 mL, half the minimal clinically important difference. The proportion of FEV_1 responders (>20% increase relative to baseline) was approximately 2.5 times higher

with oral steroids than on placebo. Effects were more prominent with higher dosages (>30 mg/d vs 7–15 mg/d), associated with more risks of side effects. Increases in walking distance were statistically significant but not clinically relevant (29 m with the 12-minute walk test), and most of these studies were short term. Some symptomatic and health status differences were reported but considered insignificant from a clinical perspective. Oral corticosteroids did not prevent exacerbations but the studies were not designed to test this end point in a robust manner.

The considerations presented here are valid only for patients with COPD and no associated asthma. The situation may be different in patients with COPD associated with predominating severe asthma, the subject of another article in this issue.

ANTILEUKOTRIENES

Antileukotriene agents are not recommended in COPD.[1] Only very few properly designed studies have been performed to assess their effects in this population. There are 2 types of available agents[18]: 5-lipoxygenase (LO) or 5-LO–activating protein inhibitors and cysteinyl-leukotrienes (Cys-LTs: LT-C4, D4, E4) receptor antagonists. Their purpose is to reduce the production of leukotrienes with proinflammatory activity (LTB4, product of the 5-LO pathway) or to decrease effects on airway smooth muscle, mucus secretion, vascular permeability, and mucociliary clearance (Cys-LTs). In 2015, 7 studies were identified, 3 of which were nonrandomized (2 with montelukast, 1 with zafirlukast). Among the 4 others, 1 dealt with zileuton (for acute exacerbations), 1 with montelukast, and 2 with products that have been secondarily abandoned. All these randomized trials were short term, whereas 2 observational studies (1 prospective, 1 retrospective) had a duration of at least 12 months.[46] Thus, from a review of all of these studies, it is clear that anti-LTs have not been properly assessed in COPD. In only 1 (short-term) randomized controlled trial (RCT) with montelukast, some nonsignificant effects on symptoms (dyspnea, sputum production) and lung function were reported.[46]

CARDIOVASCULAR/METABOLIC TREATMENTS

There is a strong interaction between COPD and cardiovascular diseases, both sharing common risk factors[10]; however, the increased cross-prevalence of these conditions is not explained simply by smoking. As mentioned earlier, this association may relate to systemic inflammation and/or decreased daily physical activity, both of which are interrelated. Impairment of cardiac function caused by lung hyperinflation may also play a role, as well as chronic or intermittent hypoxia. In addition, the burden (eg, in terms of dyspnea and exacerbations) and prognosis of COPD is impaired in the presence of cardiovascular diseases. Reciprocally, there is an increased frequency of COPD in patients with cardiovascular conditions, and COPD impairs their prognosis. Consequently, cardiovascular drugs are frequently used in patients with COPD. In addition, cardiovascular events are more frequent during and after COPD exacerbations, of which they can represent either complications or part of differential diagnoses. Because of these strong interactions, there has been a lot of interest in the potential effects of cardiovascular drugs in patients with COPD.

The first question that was raised related to the safety of β-blockers in patients with COPD: these agents, especially those with poor beta1-adrenoreceptor selectivity, can enhance airway smooth muscle contractions and, thereby worsen airflow limitation, through beta2-adrenoreceptor antagonism. In clinical trials of β-blockers for ischemic heart disease, patients with COPD were found to benefit as much as, or even more than, those with no COPD in terms of survival.[47] The effect of cardioselective β1-blockers on lung function seems very limited, if any, and these agents do not increase the occurrence of respiratory symptoms. In addition, they do not impair respiratory outcomes when continued during acute exacerbations. Observational studies had even suggested that β-blockers could decrease the risk of COPD exacerbations and related hospitalizations and mortality. However, a recent large controlled trial in the United States did not confirm this hypothesis, and found a worse outcome, including risk of death in patients randomized to receive β-blockers and who had no cardiovascular indication of beta1-blockade.[48]

Similarly, retrospective database or prospective cohort studies suggested some benefits from statins in terms of exacerbation risk. Such effects could be explained by the pleiotropic antiinflammatory effects of statins, which could control the systemic inflammation observed in many patients with COPD. However, again a randomized controlled trial did not report any effect on exacerbation rate or mortality in patients with no cardiovascular or metabolic indication.[49]

Renin-angiotensin-aldosterone system inhibitors can have antiinflammatory, antifibrotic, and antioxidant effects that could be of interest in COPD.[10] It has even been suggested that these agents have some potential to prevent

emphysema progression.[50] However, no clinical advantage related to the use of these agents has ever been formally established in adequately designed studies.

BIOLOGICS

Inflammation, oxidative stress, and airway and parenchymal remodeling, including fibrosis, all represent potential targets for biologics directed at modulating (upstream or downstream) their mediators, biological triggers, or signaling pathways. Their intimate mechanisms are involved in the clinical manifestations of COPD, including dyspnea and exacerbations, as well as in disease progression. However, this involvement is highly heterogeneous and the disease biology is still incompletely deciphered, making it difficult to identify the most relevant targets and define the corresponding patient populations. Heterogeneity applies not only to stable state but also to exacerbations. In addition, COPD is a slowly evolutive disease with an overall low reactivity to any pharmacologic intervention to date. These properties create additional hurdles when testing new agents clinically. Although clinical phenotypes correspond with clinical features or combinations of features associated with disease progression and/or treatment responses, endotypes are underlying biological mechanisms that can be identified through biomarkers.[51,52] How the disease can be split into phenotypes and endotypes is much less clear in COPD than in asthma.[53] In addition, because there is some marked overlap and discrepancies between phenotypes and between them and endotypes, the current trend is to adopt the concept of individual treatable traits that can be independently targeted by dedicated interventions.[54] Altogether, these traits cover the entire spectrum of asthma, COPD, and complex overlapping/intricate situations. Among them, eosinophilic COPD triggers particular interest.

The central role of systemic and local inflammation in COPD pathophysiology suggested that anti–tumor necrosis factor (THF) agents could have some potential to influence the natural history of the disease. In addition, TNF-alpha has been shown to induce emphysema in animal models. However, clinical trials gave disappointing results, in terms of both effects on markers of local (sputum) and systemic inflammation, and clinical outcomes.[55,56]

More recently, anti–interleukin-5 (IL-5) agents have been tested in COPD. These agents (IL-5 inhibitor or IL-5 receptor blocker) primarily target eosinophilic inflammation. In 2 parallel RCTs using mepolizumab (IL-5 inhibitor), 1 of the trials showed a reduction in the risk of COPD exacerbations (−23%) in patients with higher (>300/μL) blood eosinophil counts (considered as a reliable surrogate for sputum eosinophils).[57] However, these results were not significant in the other study. Further, there was no difference in lung function or health status in either study compared with the placebo arm. The larger and more recent study using benralizumab (IL-5 receptor blocker) did not reduce exacerbation rate in patients with eosinophilic COPD (>220 cells/μL). Therefore, additional data need to be gathered before these treatments can be recommended.

ALPHA1-ANTITRYPSIN AUGMENTATION THERAPY

Because severe alpha1-antitrypsin (AAT) deficiency is a rare disease, RCTs are difficult to conduct. A European Respiratory Society taskforce recently performed a systematic review that identified 8 RCTs and 17 observational studies (11 of which were uncontrolled) assessing the effects of augmentation therapy on various clinical and imaging outcomes.[58] Only 3 RCTs were placebo controlled. There was a beneficial effect on emphysema progression as assessed by computed tomography (CT) scan, but efficacy could not be shown in terms of clinical outcomes. However, such efficacy (although subject to more biases) was suggested by some observational studies. In addition, emphysema progression on CT scan is associated with mortality and quality of life, suggesting that it may represent a clinically relevant outcome. Therefore, several guidelines recommend augmentation therapy in AAT-deficient patients with emphysema and progressive disease.[1]

SYSTEMIC TREATMENTS FOR DYSPNEA

Dyspnea is the most important and relevant symptom of patients with COPD. It is the limiting element of exercise capacity/tolerance and daily activity. Therefore, relieving dyspnea is one of the major goals of COPD care. First-line approaches include bronchodilators and rehabilitation. Interventional techniques such as lung volume reduction can be considered in highly selected patient populations. In some patients, dyspnea remains refractory to those therapies. In such instances, benzodiazepines and morphine have been considered, but they remain seldom prescribed as part of routine practice.[59] In 2016, a Cochrane Review identified 26 RCTs with more than 500 patients with refractory breathlessness in the context of advanced disease and terminal

Table 2
Examples of systemic treatments targeting specific subpopulations/treatable traits in chronic obstructive pulmonary disease

Treatment	Subpopulation/ Treatable Trait
Established	
PDE-4 inhibitors (roflumilast)	Severe airflow obstruction, repeated exacerbations, chronic mucus hyperproduction, on top of long-acting bronchodilators
AAT	AAT deficiency
Putative	
Azithromycin	Ex-smokers, older patients, milder airflow obstruction Airway bacterial colonization/ chronic infection Repeated bacterial exacerbations
Anti–IL-5 agents	Eosinophilic COPD
Mucoactive agents	Chronic mucus hyperproduction

illness. In 14 studies, recruited subjects were primarily or exclusively patients with COPD. Altogether, the quality of evidence was deemed low or very low, but some evidence of dyspnea alleviation was found. In parallel, drowsiness, nausea and vomiting, and constipation were frequent (13%, 20%, and 18%, respectively).[60] Thus, the benefit/risk ratio needs to be carefully considered on an individual basis, balancing the risk of side effects and the burden of dyspnea. In summary, for very breathless patients, a trial can be initiated under close monitoring and stopped if the benefits are not evident or if side effects limit its use.

In a similar way, the last Cochrane Review on benzodiazepines for dyspnea was performed in 2016 and included 8 studies in patients with advanced cancer or COPD, in which benzodiazepines were compared with placebo, promethazine, or morphine. No demonstration of positive effects was found, although the investigators found less drowsiness than with morphine.

SUMMARY

Although numerous systemic treatments for COPD exist, they are positioned late in treatment algorithms, with inhaled therapy remaining the cornerstone of treatment. However, when inhaled therapy is not sufficient to control the burden of disease, oral therapies such as PDE-4 inhibitors, azithromycin, or mucoactive agents can be of help in some patients (Table 2), especially to reduce the risk of exacerbations. The major difficulty here is to choose the appropriate responder and how these treatments should be positioned in the global treatment algorithm. For instance, should they be prescribed in addition to other anti-inflammatory agents (ie, corticosteroids) or should they replace them in some specific subgroups of patients? Some currently available biologics used in severe asthma could also be effective in some patient categories (eosinophilic COPD), but additional studies centered on well-selected candidates are needed. Some oral agents, such as beta2-adrenergic agents and particularly theophylline, remain widely used in some countries because of their low cost, although their benefit/risk profiles are unfavorable compared with inhaled therapy. AAT augmentation therapy is useful in patients with AAT deficiency and progressive emphysema. Cardiovascular drugs should be used in COPD only if those patients have underlying cardiovascular condition supporting their indication. Ongoing research aims at identifying new therapeutic targets and agents in inflammation, destruction/repair mechanisms, immune regulation, microbiota homeostasis, mucus modulation, and lung regeneration.

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