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Review article

Small airway inflammation and extrafine inhaled corticosteroids plus long-acting beta$_2$-agonists formulations in chronic obstructive pulmonary disease

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ABSTRACT

Objectives: To summarize the evidence of small airways involvement in chronic obstructive pulmonary disease (COPD) pathophysiology, and to evaluate the efficacy of extrafine formulations of inhaled corticosteroids (ICS) in combination with long-acting beta$_2$-agonists (LABAs) in the treatment of COPD.
Data source: A search of the PubMed database was conducted using the keywords "COPD", "small airways", "inflammation" and "extrafine formulation." The search was limited to entries published in English before August 2016. Only studies conducted in humans were considered.
Study selection: Publications were included on the basis of relevance.
Results: COPD is a common preventable and treatable disease, characterized by persistent and progressive airflow limitation. With improved understanding of COPD pathophysiology, small airways (internal diameter < 2 mm), a well-known major site of COPD-associated inflammation and remodeling, have emerged as a potential target for COPD pharmacologic therapies. The ability of extrafine formulations of ICS in combination with LABAs to achieve central and peripheral lung deposition, and the implications of the enhanced efficacy that this may bring, are discussed by examining findings from the development trials plan of the extrafine formulation of beclometasone dipropionate/formoterol fumarate (Foster®, Chiesi Farmaceutici, Italy) in patients with COPD.
Conclusion: There is an urgent need for improved and reliable techniques for small airways assessment in order to detect early damage, disease progression and response to treatment. Evidence from randomized clinical trials supports the benefits of extrafine ICS/LABA formulations in COPD, real world studies are necessary to confirm this.

1. Introduction

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease, characterized by persistent and usually progressive airflow limitation associated with an enhanced chronic inflammatory response to noxious particles or gases in the airways and the lung [1]. The GOLD recommendations also emphasize the role of exacerbations and comorbidities as contributors to COPD severity [1]. It remains a challenging public health issue that is associated with major chronic morbidity and mortality worldwide [1,2]. COPD is currently the fourth leading cause of death worldwide, but its mortality is rising and it is expected to move to the third position by 2020 [1,2]. It is estimated that about 10% of people aged > 40 years have airflow limitation (defined as GOLD stage ≥2) and up to 25% may have undiagnosed COPD [3]. Cigarette smoke is the most common risk factor for COPD; other risk factors include occupational dusts and chemicals, and indoor air pollution from wood and biomass burning (especially in developing countries) [1].

COPD is a complex and heterogeneous disease, with airflow obstruction and a progressive decline in lung function (forced expiratory volume in 1 s, [FEV_1] as assessed by spirometry) [4,5]. Small airways, defined as those airways with an internal diameter < 2 mm, have long been known as a major site of COPD-associated inflammation and remodeling [5–7]. In the last few years, our understanding of COPD pathophysiology has been refined, and small airways have emerged as a potential target for improving inhaled pharmacologic therapies

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[6,8–12].

The goal of pharmacologic therapy in COPD is to relieve symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise performance [1]. So far, no existing COPD medication has been conclusively shown to modify the long-term clinical outcomes [1]. The most commonly used medications include long-acting inhaled bronchodilators (long-acting beta$_2$-agonists [LABAs]; long-acting muscarinic antagonists [LAMAs]; short-acting beta$_2$-agonists [SABAs]; short-acting muscarinic antagonists [SAMAs]) and inhaled corticosteroids (ICS) [1]. The 2017 GOLD guidelines recommend initiating pharmacologic treatment based on the individualized assessment of symptoms and risk of exacerbation [1]. For patients with stable COPD and a high risk of exacerbation (regardless of symptoms) a fixed combination of an ICS plus one (e.g., LABA) or more bronchodilators is one of the recommended treatments [1]. The introduction of a formulation of the fixed-dose combination of beclometasone dipropionate (BDP, an ICS) and formoterol fumarate (F, a LABA), characterized by extrafine particle size of both active components, has raised interest because of the potentially increased benefits associated with drug delivery to the small airways [13,14].

2. Objectives

This narrative review aims to discuss recent published evidence on the pathophysiology of COPD and the involvement of small airways, with an emphasis on inflammation and the role of ICS. Findings from the trial program with the extrafine formulation of beclometasone dipropionate/formoterol (BDP/F; Foster®, Chiesi Farmaceutici S. p.A., Italy) in patients with COPD are also discussed.

3. Methods

3.1. Data source

The literature discussed in this review was identified by searching the PubMed database (up to August 2016) for English-language publications using the keywords “COPD”, “small airways”, “inflammation” and “extrafine formulation”. Only studies conducted in humans were considered.

3.2. Study selection

Publications were included based on relevance.

4. COPD complexity

4.1. Pathogenesis and pathophysiology

Both small airways disease and parenchymal destruction are responsible for the chronic airflow limitation characteristic of COPD, with relative contributions of these two components varying between individuals [1,5,9]. COPD results from the interplay between genetic susceptibility and exposure to environmental stimuli. Among environmental stimuli, cigarette smoking is the main cause of the pathology [1], other factors, such as outdoor air pollution, occupational exposure to dusts and fumes, second-hand smoke, and biomass smoke inhalation, might increase the risk of and lead to disease in non-smokers [1].

Airway inflammation, involving a variety of cells, such as neutrophils, eosinophils, macrophages and lymphocytes, plays a major role in COPD pathogenesis [15–19]. Normal inflammatory responses are amplified in COPD patients, for reasons that are not yet fully understood, although genetic factors are likely to be involved. It has been recently found that three significant loci on chromosome 2q and 10q are associated with airway wall thickness in heavy smokers [20]. Beside inflammation, other pathogenic mechanisms underlying COPD include oxidative stress and protease-antiprotease imbalance (resulting in elastin degradation; elastin is a major component of lung parenchyma) [1,21,22].

Exposure to oxidants in cigarette smoke causes direct injury to epithelial cells of airways leading to airway inflammation [23]. In the absence of adequate repair mechanisms, such as antiproteases and antioxidants, subsequently released proteolytic enzymes and reactive oxygen species (ROS) produce further damage. Typically, ROS (e.g., free oxygen radicals, such as superoxide anion and hydroxyl radicals, and hydrogen peroxide) are continually formed in cells during normal metabolic processes, but in the airways of COPD patients, large quantities of ROS are produced by activated phagocytic cells when stimulated during the inflammatory processes [23,24]. Such large quantities of ROS result in oxidative stress leading to harmful effects, namely damage to lipids, proteins and DNA [23]. Chronic inflammation causes structural changes and narrowing of the small airways [6,10,22,25–27]. Chronic inflammation also causes destruction of the lung parenchyma, leading to the loss of alveolar attachments to the small airways, and of lung elastic recoil [6,10]. These changes also impair the ability of small airways to remain open during expiration. How small airways disease and emphysema result in the physiologic abnormalities and symptoms of COPD is fairly well characterized: there is a clear correlation between small airways changes and decline of spirometry parameters (FEV_1) [10]. Small airways obstruction progressively traps air during expiration, resulting in hyperinflation; emphysema also contributes to air trapping [1,28]. Hyperinflation reduces inspiratory capacity, particularly during exercise (dynamic hyperinflation), resulting in increased dyspnea and limited exercise capacity; hyperinflation has been reported to be associated with increased mortality [1,5,28–32].

Some studies have evaluated closing volume (CV) in relation with the expiratory reserve volume (ERV), as an important indicator of potential small airways damage. A high percentage of COPD patients have CV > ERV, which is indicative of cyclic opening and closure of small airways during tidal breathing, and this mechanical stress exposes the patient to increased small airways inflammation and, in the long term, to peripheral lung damage [33,34].

4.2. Involvement of the small airways

Small airways are defined as those with an internal diameter < 2 mm; they are located from the eighth generation of airways and account for 98.8% of the total lung volume [8]. Small airways have peculiar anatomic and physiologic features that are relevant for COPD pathogenesis. Compared with proximal airways, small airways in healthy individuals have an elevated total cross-sectional surface area, with a low total bronchial resistance (< 10%), laminar airflow (vs. turbulent airflow in proximal airways), membranous bronchioles and gas exchange ducts, a high density of beta$_2$-adrenergic receptors involved in bronchodilation (vs. a low receptor density in proximal airways), an absence of cartilaginous structures, and a marked presence of smooth muscle. Similar to proximal airways, small airways have a high density of corticosteroid receptors [5,7,35,36].

Progress in our understanding of the role of small airways in respiratory diseases has been hampered by the lack of appropriate tools for the assessment of their structure and function [5,8]. The need for reproducible, non-invasive, validated assessment tools and markers for evaluating small airways disease is widely recognized. A number of new and potentially useful methods have emerged in recent years, including impulse oscillometry, multiple-breath nitrogen washout, exhaled nitric oxide, and imaging techniques (Table 1) [8]. In a recent publication, the Interasma (Global Asthma Association-GAA) and World Allergy Organization (WAO) state that functional and biological tools that can accurately assess small airways are needed in order to improve patient phenotyping and provide appropriate treatment for COPD [37].

In a recent population-based study, total airway count on computed tomography (CT) was found to reflect small airway-related disease changes during early or mild COPD, indicating that this parameter is a

Table 1
Small airway assessment methods (table adapted from Bonini et al., 2015 [8]).

Method	Parameters measured	Outcome	Advantages	Disadvantages
Noninvasive techniques				
Spirometry	FEV_3, FEV_6, FVC, FVC/SVC, FEF_{25-75}	• Air trapping • Ventilation heterogeneity	• Easy to perform • Widely available	• Influenced by large airways obstruction and volume changes
Body plethysmography	TLC, FRC, RV	• Air trapping • Ventilation heterogeneity	• Easy to perform • Widely available	• Further studies required
Single breath nitrogen washout	CV, CC	• Air trapping • Ventilation heterogeneity	• Good sensitivity and reproducibility	• Not widely available
IOS	Resistance, reactance, impedance	• Air trapping • Ventilation heterogeneity	• Simple • Good reproducibility	• Not widely available
MBN_2W	S_{acin}, S_{cond}	• Air trapping • Ventilation heterogeneity	• Good sensitivity and reproducibility	• Not widely available • Complex technique
Exhaled NO at multi-flow	FeNO, CAlvNO	•Inflammation •Remodeling	•No diurnal variation reproducibility	•Computational extrapolation required
Sputum induction	Inflammatory markers	• Inflammation • Remodeling	• Direct assessment	• Poor reproducibility and standardization
HRCT	Lung attenuation	• Air trapping • Ventilation heterogeneity	• High resolution	• High costs • Exposure to radiations
MRI with inhaled hyperpolarized gases	Lung attenuation	• Air trapping • Ventilation heterogeneity	• High resolution • No radiations	• Not widely available • Complex technique
Nuclear imaging (PET, SPECT)		• Air trapping • Ventilation heterogeneity	• High resolution	• High costs • Exposure to radiations
Invasive techniques				
Transbronchial biopsy	Tissue specimens	• Inflammation • Remodeling	• Direct assessment	• Invasive
BAL	Cellularity	• Inflammation • Remodeling	• Direct assessment	• Invasive
Esophageal balloon	P-V curve	• Air trapping	• Direct assessment	• Invasive

Abbreviations: CAlvNO, alveolar concentration of nitric oxide; CC, closing capacity; CV, closing volume; FEF_{25-75}, flow between 25% and 75% of the FVC; FeNO, exhaled fraction of nitric oxide; FEV, forced expiratory volume (in 3 or 6 s); FRC, functional residual capacity; FVC, forced vital capacity; IOS, impulse oscillometry; HRCT, high-resolution computed tomography; MBN_2W, multiple-breath nitrogen washout; MRI, magnetic resonance imaging; PET, positron emission tomography; P-V, pressure volume; RV, residual volume; S_{acin}, ventilation inhomogeneity in acinar airway regions; S_{cond}, ventilation inhomogeneity in conducting airway regions; SPECT, single photon emission computed tomography; SVC, slow vital capacity; TLC, total lung capacity.

potential biomarker of COPD progression [38]. In another study of small airway pathology in COPD lungs, multidetector row CT showed decreases in the number of 2–2.5 mm diameter airways and the lumen of fifth generation airways on, while microCT demonstrated decreases in the number of terminal bronchioles (TB) and the lumen, wall volumes and alveolar attachments of preterminal (TB-1) and pre-preterminal bronchioles (TB-2) [39]. MicroCT and histology also showed increased B cell infiltration of TB-1 and TB-2 walls, which correlated with a decreased number of alveolar attachments. These findings suggest that small airway-related disease changes extend from 2-mm diameter airways to the TBs, and that a B cell-mediated immune response may lead to the loss of alveolar attachments [39].

Fractional exhaled nitric oxide (FeNO) is a direct reliable marker of airway eosinophilia that is routinely measured in clinical practice and used for follow-up evaluations. Its main application is in patients with asthma, but recent studies have evaluated its usefulness in COPD mainly for prediction of exacerbations and the need for ICS. As with asthma, FeNO levels in patients with COPD are influenced by airway bronchoconstriction [40]. Alveolar nitric oxide (NO) is elevated in patients with COPD, independent of smoking status and disease severity [41] and FeNO does not appear to be associated with COPD severity [42]. Patients with stable COPD who have persistently elevated FeNO ($\geq$20 parts per billion) seem to have a higher risk of an acute exacerbation [43]. Airway eosinophilic inflammation evaluated by FeNO in patients with COPD is not correlated with systemic inflammation [43]. Although FeNO and/or alveolar NO evaluation seem to be potentially useful tools for COPD management, more data are needed to support their routine clinical use.

Studies documenting the involvement of small airways in respiratory diseases date back to the early 1960s [44,45]; however, compelling evidence supporting the correlation between small airways disease/changes and COPD severity and airflow limitation comes from more recent studies [10,22,46–49]. In particular, both narrowing of small airways and their reduction in number have been shown to contribute to the rapid decline of FEV_1 in COPD, and loss of distal bronchioles precedes the onset of emphysema. Pathological abnormalities are observable in histological samples of small airways from young non-obstructed smokers that show membranous bronchioles with damaged epithelium and higher number of wall inflammatory cells. Taken together, these data suggest that the pathologic process begins in the small airways in the early stages of COPD [22]. Moreover, many studies show high prevalence of small airways abnormalities (74–90%) among COPD patients [27,50]. These findings provide a rationale for the use of small-particle formulations to target those areas where the disease starts. The effects of small airways changes on COPD progression and survival have been investigated [11,51–53]. Small airways disease is associated with reductions in FEV_1 [11,53], and the severity of small airways disease, determined on the basis of lung biopsy samples collected after volume reduction surgery in patients with severe emphysema, has been associated with early death [11]. Small airways disease also has an impact on patient-reported outcomes, with a strong association demonstrated between the severity of small airways disease and

quality of life and dyspnea [50,54]. In a study conducted by Han and colleagues, functional abnormalities in small airways, detected by high-resolution computed tomography, have been shown to correlate with the frequency of acute COPD exacerbations [55].

4.3. Outcomes of pharmacologic therapy delivered to the small airways

Fixed-dose ICS/LABA is a recommended treatment for patients with COPD who are at risk of exacerbations [1,14]. Bronchodilators improve spirometry parameters by altering the tone of airway smooth muscle, while ICS reduce inflammation [1]. Based on the findings of multiple studies regarding lung function, symptoms, exacerbation rate, and the general health status, synergistic interaction has been suggested, with increased efficacy of the combination compared with the individual components [14,56–64].

Particle size is a critical factor determining the therapeutic efficacy of inhaled drugs. The mass median aerodynamic diameter (MMAD) is used to measure the heterogeneity of particles in an emitted dose. MMAD predicts the deposition and distribution of particles in the bronchial tree. Using radiolabeled salbutamol, Usmani and colleagues demonstrated an inverse relationship between particle size and lung deposition. Lower MMAD reduces oral deposition, thereby attenuates the consequences of an incorrect inhalation technique [65]. Inhaled formulations with MMAD $< 2\,\mu m$ have been termed “extrafine” [1,66]. The extrafine fixed-dose ICS/LABA (BDP/F 100/6 μg) for use in asthma and COPD was developed by Chiesi Farmaceutici S. p.A. using a pressurized metered dose inhaler (pMDI) and a dry powder inhaler (DPI). Extrafine BDP/F achieves central and peripheral lung deposition, leading to increased potential for synergistic interaction and improved efficacy (Fig. 1) [67–69]. A study conducted using functional respiratory imaging has shown that treatment with extrafine BDP/F improves small airways geometry and reduces hyperinflation [68]. Distribution of extrafine BDP/F is not affected by the degree of obstruction in the airways, resulting in similar lung deposition in healthy volunteers and patients with asthma and COPD, despite different FEV_1 values [69]. Taking into account the central role of small airways in the pathogenesis of COPD, formulations reaching both the proximal and the distal zone of the lung are likely to provide additional advantages compared to traditional formulations.

Head-to-head studies have compared the extrafine BDP/F combination with other non-extrafine combinations in the market [70–72]. Although the comparative treatments showed no difference in classical lung function parameters and symptomatology, there were signs of greater efficacy in the peripheral airways or of a qualitatively better symptomatic response in all the studies. Several studies have examined the effects of extrafine BDP/F formulations on small airways in patients with COPD. Extrafine BDP/F has been shown to improve forced vital capacity (FVC) from baseline compared with F only and a non-extrafine BUD/F combination [70]. Extrafine BDP/F also demonstrated greater efficacy in reducing several measures of hyperinflation (residual volume, total lung capacity and functional residual capacity) compared with fluticasone propionate/salmeterol (FP/S) [72]. Patients treated with extrafine BDP/F experienced a statistically significant improvement in transition dyspnea index (TDI) total score from baseline, which exceeded the threshold for clinical relevance (+1 points) [72]. Taken together, these studies suggest that extrafine combinations are effective in addressing peripheral obstruction, reducing airtrapping and hyperinflation that worsen symptoms, quality of life and mortality in COPD [29]. Clinically, this translated into better performance and exercise capacity, with patients with COPD who were treated with BDP/F having significantly greater improvement in the 6 min walking test (6-MWT), which exceeded the threshold for clinical significance (37 m). This improvement was likely due to reduced airtrapping [70,73].

The superiority of extrafine BDP/F formulation to F alone has been demonstrated in a phase III, double-blind, randomized, parallel-group study (FORWARD), conducted in patients with severe COPD and a history of exacerbations. Patients who received extrafine BDP/F experienced greater improvements than those who received F alone in the co-primary endpoints of exacerbation rate over 48 weeks and pre-dose morning FEV_1 at 12 weeks (by 28% and 0.069 L, respectively) [74]. In another study, extrafine BDP/F was compared with non-extrafine FP/S DPI in patients with COPD. Both treatments were associated with improvements in dyspnea (TDI score) and quality of life (St. George's respiratory questionnaire [SGRQ] score), but the threshold for clinical relevance of SGRQ (> 4 units) was achieved only with the extrafine BDP/F combination. In addition, extrafine BDP/F showed faster onset of action, which was observed after the first dose and maintained throughout the entire study period (12 weeks). This is especially beneficial because early morning symptoms are very common in patients with COPD and rapid bronchodilation improves physical exercise tolerance upon awakening [75]. The medium daily dose of BDP/F used in

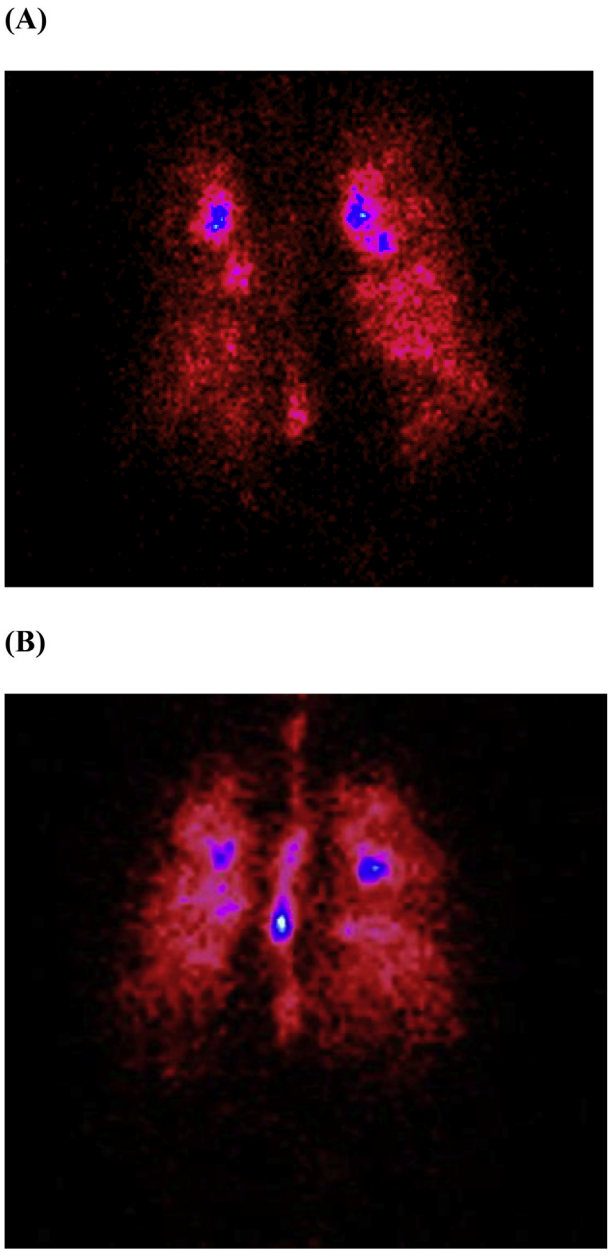

Fig. 1. Scintigraphic lung deposition in COPD patients after inhalation of (A) extrafine BDP/F NEXThaler® 100/6 μg DPI and (B) extrafine BDP/F 100/6 μg pMDI. Studies conducted by radiolabeling ^{99}mtechnetium and images were taken with a planar γ camera. From data on file Chiesi Farmaceutici S. p.A.

the study was lower (400 μg) than the medium daily dose of FP/S (1000 μg), according to the GINA table of equivalent ICS doses [71,76]. This comparison may seem contrived due to absence of clear equivalence of ICS doses in GOLD recommendations, but the fact that side effects of ICS are dose-dependent must be considered [77,78]. In patients with COPD, the FP/S combination is indicated at a high dose in Europe (daily dose 1000/100 μg), while only the medium dose (daily dose 500/100 μg) is approved in the US, because the efficacy advantage of the higher dose had not been demonstrated [79].

5. Inflammatory response in COPD

COPD is a complex disease characterized by both systemic and airways inflammation [4]. In particular, patients with COPD have high levels of serum C-reactive protein (CRP); high numbers of neutrophils, eosinophils, macrophages and lymphocytes in bronchial biopsies; and a high percentage of neutrophils and eosinophils in sputum and bronchial wash [80–86]. However, the inflammatory cascade involved in COPD is poorly understood [87].

5.1. Inflammatory cells and mediators in small airways

Chronic inflammation leading to small airway narrowing and emphysema in COPD, is characterized by an increased number of macrophages, neutrophils, eosinophils, and cytotoxic $CD8^+$ T-lymphocytes (increased in both large and small airways, as well as in lung parenchyma) [5,10,80,88,89], and the release of multiple inflammatory mediators including lipids, chemokines, cytokines, and growth factors [88,90]. Moreover, large numbers of lymphoid follicles are present in the small airways with more severe stages of COPD, probably the result of an adaptive immune response due to colonization and infection of the lower airways that occurs because of the increase in lymphocytes and their organization into lymphoid follicles [10].

5.2. Inflammation and COPD exacerbations

COPD exacerbations are defined as acute events characterized by worsening of respiratory symptoms beyond normal day-to-day disease variations and which lead to a change in treatment [1]. Frequent exacerbations are associated with a more rapid decline of FEV_1 [21,91]; they are life threatening, and associated with worse prognosis and higher mortality rates [92–94]. Increased numbers of neutrophils and eosinophils in sputum or bronchial tissue have been associated with an increased risk of exacerbations. In addition, during exacerbations all cells involved in the inflammation process increase in concentration in the bronchial environment [95–99].

6. Role of inhaled corticosteroids in COPD

In both extrafine and non-extrafine formulations, the corticosteroid component of the ICS/LABA combinations warrants further investigation. While ICS are highly effective in most patients with asthma, the effects of ICS on inflammation and its benefit/risk ratio in COPD are controversial [1,100]. Although some studies have failed to demonstrate any anti-inflammatory efficacy [101–103], a number of studies suggest a favorable impact of ICS on systemic and airway inflammation in patients with COPD [11,104–108].

Results from randomized controlled [59,64,109–111] and real-world [112] studies investigating the efficacy of ICS on respiratory symptoms, exacerbations and mortality in COPD patients have been mixed. In the COSMIC [110] and WISDOM [111] studies, withdrawal of ICS was associated with significant decreases in lung function. A study by Lapperre and colleagues [109], the SUMMIT [64] and the TORCH studies [59] demonstrated reductions in lung-function decline or improvements in lung function with ICS therapy. In the TORCH and SUMMIT studies, ICS/LABA therapy was also associated with significant benefits with regard to exacerbation frequency, with non-significant reductions in mortality risk [59,64]. Interestingly, a real-world study found that addition of ICS to LABA therapy provided significant reductions in mortality rates among patients with moderate-to-severe COPD ($P = 0.024$), particularly those with frequent exacerbations [112]. A meta-analysis of randomized controlled trials indicated that exacerbation rates were lower with ICS/LABA than LABA alone, while mortality rates showed no significant difference between the two treatments [113].

ICS use has been reported to be associated with an increased risk of pneumonia in some studies, although the risk of mortality due to pneumonia does not increase, and in fact, ICS treatment seems to be protective against this risk [77,114,115]. However, the risk factors for acquiring pneumonia are often the same as those that mandate the use of ICS combination treatment in patients with COPD [77,114,115]. In addition, severe acute exacerbations of COPD have an independent negative impact on patient prognosis. Mortality increases with the frequency of exacerbations requiring hospitalization, and the mortality rate among patients with COPD during hospital stay was 8%, increasing to 23% after 1 year of follow-up [93,94]. European Medicines Agency (EMA) has recently reviewed the known risk of pneumonia associated with ICS use in COPD. EMA confirmed that patients with COPD who are treated with ICS have an increased risk of pneumonia, but concluded that the benefits of inhaled corticosteroids continue to outweigh their risks [116]. A retrospective cohort study of 23,013 patients with obstructive lung disease, aimed to compare the risk of pneumonia and other adverse respiratory consequences between non-extrafine ICS and extrafine ICS, demonstrated that patients using non-extrafine ICS, if switched to extrafine ICS therapy, are significantly less likely to have pneumonia and adverse respiratory outcomes. This more favorable benefit/risk ratio could be linked to the characteristics of the formulation that allow dose optimization, with a lower oropharyngeal deposition and a better distribution in the entire bronchial tree [117,118].

7. Conclusions and perspectives

COPD is a complex and heterogeneous disease. Small airways are a major site of inflammation where structural abnormalities result in progressive airflow limitation. Small airways disease may be present in asymptomatic patients and precede COPD development. ICS/LABA have been shown to improve lung function, reduce functional decline and the frequency of exacerbations, and improve the quality of life in patients with COPD. Further improvements were shown with extrafine particle formulations, as they are able to reach both central and peripheral areas of the lung and, therefore, the principal site of inflammation and obstruction in COPD. In order to detect early damage, disease progression and response to treatment, the possibility of developing a feasible composite score for the assessment of the small airways should be evaluated. There is a substantial amount of published evidence regarding the clinical benefits of extrafine ICS/LABA combinations, in terms of clinical outcomes. Considering the pathophysiology of COPD, extrafine ICS/LABA combinations could be a valid therapeutic option, and, although evidence from randomized clinical trials supports these benefits, real world studies are necessary to confirm this in routine practice.

Conflicts of interest

Davide Paleari is an employee of Chiesi Farmaceutici SpA, Italy. Pietro Pirina, Maria Pia Foschino Barbaro and Antonio Spanevello declare no conflicts of interest.

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Author contributions

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