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REVIEW

Beyond corticosteroids: future prospects in the management of inflammation in COPD

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ABSTRACT: Inflammation plays a central role in the pathophysiology of chronic obstructive pulmonary disease (COPD). Exposure to cigarette smoke induces the recruitment of inflammatory cells in the airways and stimulates innate and adaptive immune mechanisms. Airway inflammation is involved in increased bronchial wall thickness, increased bronchial smooth muscle tone, mucus hypersecretion and loss of parenchymal elastic structures. Oxidative stress impairs tissue integrity, accelerates lung ageing and reduces the efficacy of corticosteroids by decreasing levels of histone deacetylase-2. Protease–antiprotease imbalance impairs tissues and is involved in inflammatory processes. Inflammation is also present in the pulmonary artery wall and at the systemic level in COPD patients, and may be involved in COPD-associated comorbidities.

Proximal airways inflammation contributes to symptoms of chronic bronchitis while distal and parenchymal inflammation relates to airflow obstruction, emphysema and hyperinflation. Basal levels of airways and systemic inflammation are increased in frequent exacerbators.

Inhaled corticosteroids are much less effective in COPD than in asthma, which relates to the intrinsically poor reversibility of COPD-related airflow obstruction and to molecular mechanisms of resistance relating to oxidative stress. Ongoing research aims at developing new drugs targeting more intimately COPD-specific mechanisms of inflammation, hypersecretion and tissue destruction and repair. Among new anti-inflammatory agents, phosphodiesterase-4 inhibitors have been the first to emerge.

KEYWORDS: Chronic obstructive pulmonary disease, inflammation, mucus hypersecretion, phosphodiesterase-4 inhibitors, repair, treatment

Inflammation is unanimously agreed to play a central role in chronic obstructive pulmonary disease (COPD) pathology, but is less responsive to corticosteroids than asthma, in which the characteristics of inflammation are different. Over the past 15 yrs, the development of exercise rehabilitation, new molecules to help smoking cessation and various drugs (including β2-agonist or anticholinergic long-acting bronchodilators, and fixed combinations of long-acting β2-agonists and corticosteroids) has led to significant progress in COPD management. Indeed, long-acting bronchodilators represent the first line of pharmacological COPD treatment and are of value in all patients who require symptom relief or prevention on a regular basis. Both β2-agonists and anticholinergic agents have been shown to exert anti-inflammatory effects *in vitro*. However, the clinical relevance of these effects is not clear, which does not prevent them from being effective at improving respiratory mechanics, relieving dyspnoea, increasing exercise tolerance, preventing exacerbations and improving quality of life [1–3]. Effects on lung function decline and mortality remain a matter of debate [1, 2].

Even so, several needs are still largely unmet: the impairment in quality of life due to dyspnoea-related reduction in exercise tolerance and exacerbations remains incompletely controlled by current treatments, which are unable to reverse anatomic airway (remodelling) and parenchymal lesions (emphysema).

Pharmacologic progress in COPD will depend on improved knowledge of the pathophysiology of the disease and consequent biological and clinical phenotypes. In November 2009, a group of 18 French-speaking COPD experts met to discuss the

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relationships between inflammation and COPD and possible new tools to treat COPD inflammation [4–6].

COPD AND INFLAMMATION: THE RELATIONSHIP IS CERTAIN BUT INCOMPLETELY UNDERSTOOD

It is now clear that the development of COPD is associated with chronic bronchial and pulmonary inflammation. Inhaled toxic gases and particles, generally from cigarette smoke (primary cause of COPD), target the bronchial and alveolar epithelium, activating it and inducing recruitment of inflammatory and immune cells in the bronchial mucosa and deep lung [7]. The presence of nonspecific (neutrophils and macrophages) and adaptive (T-lymphocytes) immune cells and their persistence even after smoking cessation [8] suggests that, in some predisposed subjects, cigarette smoke directly or indirectly stimulates memory cells of adaptive immunity [9]. In patients with COPD, lung infiltration by dendritic cells contributes to maintaining an inappropriate adaptive immune response which induces chronic inflammation and lung tissue remodelling. Indeed, expression of co-stimulatory molecules at the surface of dendritic cells correlates with COPD severity (Global initiative for Chronic Obstructive Lung Disease (GOLD) classification) [10]. In COPD patients, mature lymphoid follicles with a germinal centre and well defined T- and B-lymphocyte areas in the peribronchiolar tissue reflect this adaptive immune response. B-lymphocytes isolated from these follicles are oligoclonal, suggesting antigen-specific induction [11, 12]. The antigens underlying these immune responses may be microbial antigens, cigarette smoke components, or auto-antigens related to epithelial or extracellular matrix degradation products.

The relationship of inflammation to structural and functional abnormalities has been consistently confirmed [8]. Airway inflammation alters bronchial structure–function relationships in COPD patients *via* four main mechanisms, the relative importance of which varies from patient to patient: 1) increased bronchial wall thickness, 2) increased bronchial smooth muscle tone, 3) mucus hypersecretion, and 4) loss of elastic structures (fig. 1). These abnormalities are mainly induced by a protease/antiprotease imbalance and oxidative stress, which also reduces the effect of corticosteroids on the cellular inflammation and cytokine levels in COPD patients' airways.

Oxidative stress is defined by an oxidant–antioxidant imbalance. It plays an important role in the induction and persistence of tissue damage in COPD [14]. There are multiple sources of reactive oxygen species: environmental (*e.g.* smoking), local (activated alveolar macrophages and neutrophils), and intracellular (aerobic metabolism controlled by mitochondrial respiration). In this sense, oxidative stress is an adaptive response triggering the immune response by nuclear factor-κB and activator protein-1 activation, so as to neutralise infectious agents and conserve intracellular redox balance, notably *via* the glutathione system [15]. Intense and persistent oxidative stress over the long term, however, impairs tissue integrity through various mechanisms, including protease/antiprotease imbalance, accelerated ageing, lipid peroxidation and vascular endothelial growth factor pathway alteration. Thus, reactive oxygen species are implicated in: mucus hypersecretion and impaired mucociliary clearance; fibroblast proliferation and

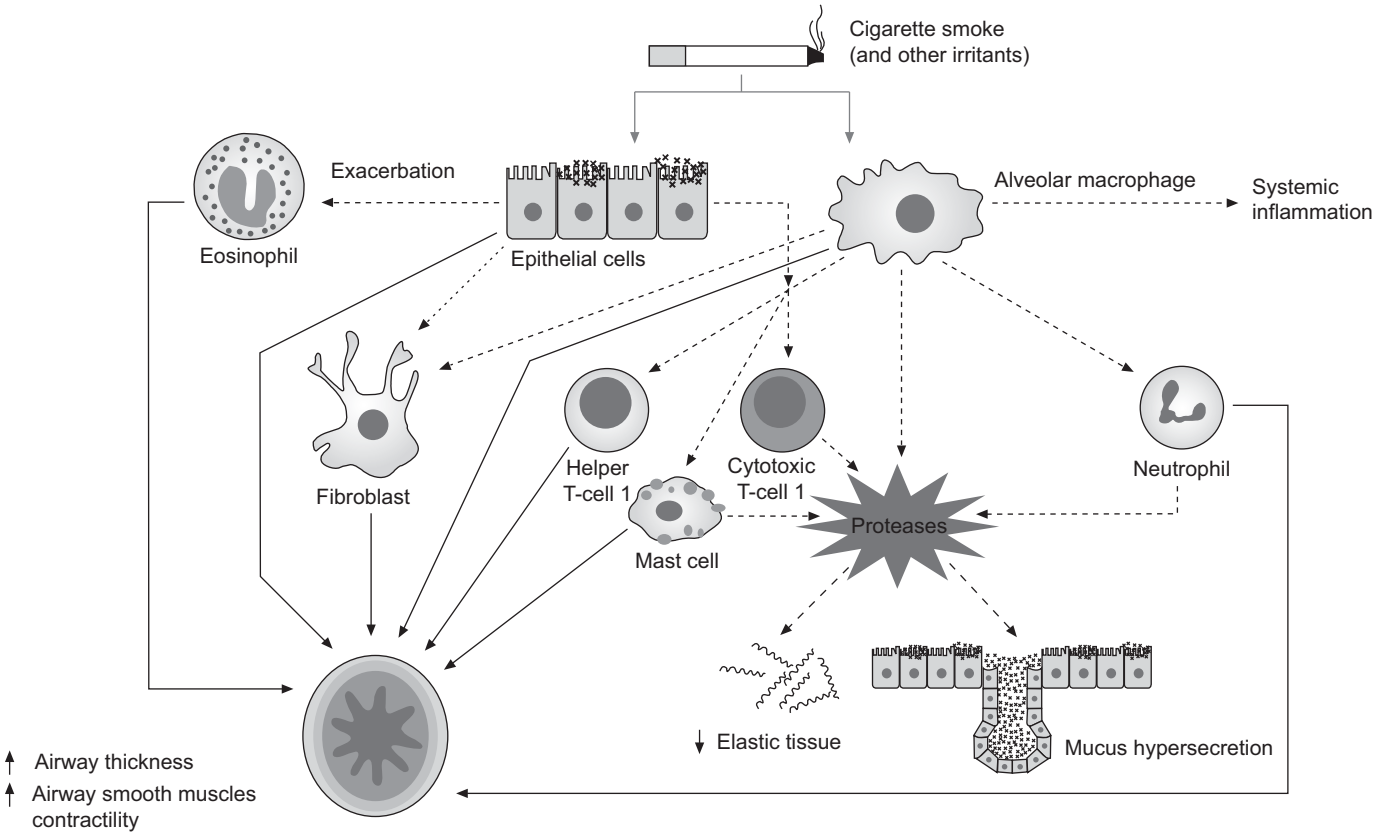

FIGURE 1. The four main pathophysiological mechanisms involved in the alteration of bronchial structure–function relationships in chronic obstructive pulmonary disease patients. Modified from [13] with permission from the publisher.

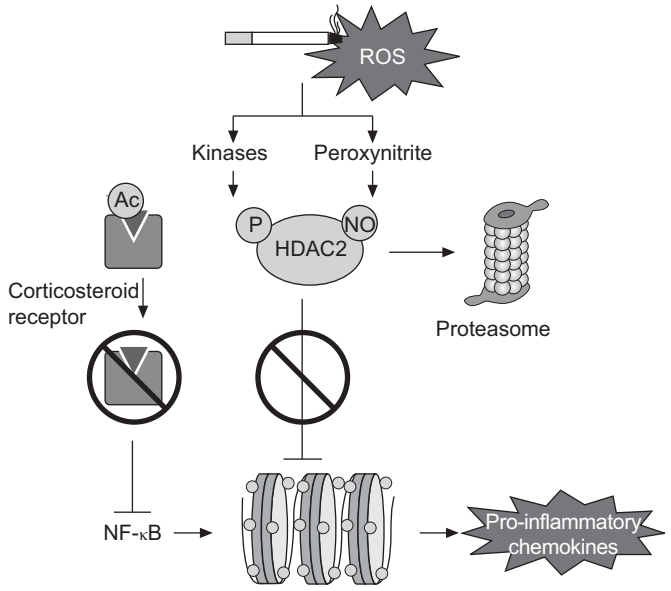

FIGURE 2. Oxidative stress and corticoresistance. Stimulation of alveolar macrophages by pro-inflammatory stimuli activates nuclear factor (NF)-κB and other transcription factors to switch on histone acetyltransferase, leading to histone acetylation and, subsequently, transcription of genes encoding pro-inflammatory chemokines. Corticosteroids reverse this by binding to glucocorticoid receptors and recruiting histone deacetylase (HDAC)2. In chronic obstructive pulmonary disease patients, cigarette smoke generates oxidative stress (acting through the formation of peroxynitrite). This impairs the activity of HDAC2. Consequently, the inflammatory response to NF-κB activation is amplified, and the anti-inflammatory effect of corticosteroids is reduced. ROS: reactive oxygen species. Modified from [17] with permission from the publisher.

extracellular matrix destruction; endothelial cell apoptosis; and triggering of the inflammation response. The determinants of extra- and intracellular redox control, which involve the mitochondrial function and antioxidant systems, are only partially known. Susceptibility genes and insufficient antioxidant system response with reduced levels of anti-ageing molecule are probably involved to varying degrees in accelerated progression of COPD. Indeed, oxidative stress accounts for certain similarities observed between the respiratory system alterations observed in COPD and cell ageing [16]. Finally, inflammatory cells (*e.g.* alveolar macrophages) in patients with COPD induce histone acetylase/deacetylase system dysfunction, which is sensitive to redox balance (fig. 2). As a consequence, reduced levels of histone deacetylase (HDAC)2 contribute to the impairment of cellular response to the anti-inflammatory effects of corticosteroids, which has been observed in several *in vitro* studies [17].

While it is generally agreed that COPD inflammation is not restricted to the respiratory system, the relationships between pulmonary and systemic inflammation remain poorly known. However, the presence of some specific pulmonary inflammation markers in the bloodstream suggests extrapulmonary spread, although the respiratory and circulating levels of some mediators are not correlated. Previous studies have long shown increased plasma concentrations of inflammation markers (*e.g.* tumour necrosis factor (TNF)-α) and other nonspecific mediators, such as acute-phase proteins (*e.g.* interleukin (IL)-6). The severity of systemic inflammation increases over time and with COPD exacerbations [18]. Systemic inflammation may be involved, to some degree, in the occurrence of some comorbidities associated with COPD, such as sarcopenia, diminished exercise tolerance, cardiovascular impairment, osteoporosis, anaemia, diabetes or depression.

Considering all the previously mentioned mechanisms, the molecular and cellular targets of inflammation and remodelling in COPD are many and various (table 1).

COPD AND INFLAMMATION: DIFFERENT MECHANISMS FOR DIFFERENT PHENOTYPES

The COPD population is notoriously heterogeneous. The variability in the risk of developing COPD and the number of different phenotypes argue for an individual genetic component; pangenomic studies have confirmed the importance of the antioxidant systems and the role of genes involved in angiogenesis. Cohort studies sought to distinguish patient phenotypes in terms of presenting characteristics and clinical evolution [19]. These phenotypes might be particularly associated with specific pathophysiological mechanisms responsive to some existing or expected treatments.

Although the differences between COPD with and without associated chronic bronchitis are not fully understood, proximal bronchial inflammation is associated with chronic bronchitis

TABLE 1 Major promising molecular and cellular targets of inflammation and remodelling in chronic obstructive pulmonary disease

Targets categories	Examples of target
Transcription factor and second messenger	Nuclear factor-κB, chromatin, histone acetylase/histone deacetylase, mitogen-activated protein kinases and phosphoinositide 3-kinase inhibitor, haem oxygenase-1
Oxidative metabolism and phospholipides	Endogenous anti-inflammatory mediators such as lipoxins or resolvins, microsal epoxide hydrolase, glutathione *S*-transferase, haem oxygenase-1, *etc*.
Mediators	Elastase, matrix metalloproteinase, cytokines, growth factors
Inflammatory cells	Cytokines, chemokines, interleukin-8 receptor-β (CXCR2)
Resident cells (dendritic cells, macrophages, mastocytes)	
Neutrophils, eosinophils	
B-lymphocytes	
Structural epithelial cells	

while small airway inflammation and remodelling correlate strongly with severity of obstruction. In smokers with COPD, central airway submucosal infiltration by macrophages and T-lymphocytes (mainly CD8+) on bronchial biopsy is greater than in chronic bronchitis without obstructive respiratory disorder; more neutrophils are also found in the bronchial lumen [20, 21]. Furthermore, subjects with severe emphysema, compared to subjects without COPD, more often demonstrate tissue and lumen infiltration by various inflammatory cells (neutrophils, eosinophils, macrophages, and CD4 and CD8 T-lymphocytes) and a significant elevation in cells expressing adenovirus E1A protein, possibly implicating viral infection in the inflammatory infiltrate [22]. Airway computed tomography (CT) helps distinguishing two types of patients according to whether bronchial obstruction or emphysema predominates: areas of weak pulmonary attenuation on CT, corresponding to emphysema, and bronchial wall thickening, correlating independently with measures of pulmonary obstruction [23]. There also seems to be a relationship between inflammation and bronchial and pulmonary lesions on the one hand, and dynamic hyperinflation on the other. A correlation was also demonstrated between elevated residual volume at rest and sputum neutrophilia with bronchial CD45+ cell infiltration [24, 25].

Exacerbation is a significant event in the course of COPD: patients may therefore be distinguished in terms of exacerbation history. The mean incidence of exacerbation varies from 0.5 to 3.5 per patient per year in published studies; so-called "frequent exacerbators" in general experience at least two exacerbations per year. Persistent elevated baseline inflammation (local and systemic) appears to be associated with frequent exacerbations. Other risk factors deserve investigation in cohort studies, such as mucus hypersecretion, degree of emphysema and hyperinflation, lower airway bacterial colonisation, characteristics of lower airway inflammation, COPD GOLD stage and other predictors of outcomes like the BODE index (body mass index, airflow obstruction, functional dyspnoea, exercise capacity), health-related quality of life and genetic factors [26–30].

Inflammatory cells, the number of which correlates with the degree of pulmonary endothelial dysfunction, are also found in the pulmonary artery wall of COPD patients, and the risk of pulmonary hypertension increases with the severity of low-grade systemic inflammation [31, 32]. The role of low-grade chronic inflammation in COPD comorbidity and, especially, in nutritional and muscular impairment, remains a matter of debate.

Altogether, although COPD is systematically associated with chronically impaired airflow, the causal mechanisms vary and the classic dichotomy between bronchial disease and emphysema is certainly an oversimplification.

COPD AND INFLAMMATION: NEW DATA FOR NEW TREATMENTS

Inhaled corticosteroids are recommended for the treatment of COPD only in combination with long-acting β2-agonists, when forced expiratory volume in 1 s (FEV_1) is <50% predicted (60% pred for the salmeterol-fluticasone combination according to European marketing authorisation) and when there is a history of frequent exacerbations. Although some *in vitro* studies found that in COPD patients (except those with asthma-like eosinophilic inflammation) [33] airway inflammation is much less sensitive to corticosteroids than in asthma (which may be due to several factors including decreased HDAC-2 activity) (table 2 and fig. 2) [17, 34], others demonstrated that these agents are able to reduce sputum neutrophils [35] and (at least when associated with long-acting β2-agonists) decrease airway inflammation as assessed by bronchial biopsies [36]. Molecular co-operation between corticosteroids and β2-agonists appears to be bidirectional, with corticosteroids increasing the transcription of the β2-adrenoreceptor gene while β2-agonists increase nuclear translocation of the glucocorticoid receptor following ligand fixation [37]. Clinically, the TORCH study (TOwards a Revolution in COPD Health) showed that inhaled corticosteroids associated with long-acting β2-agonists decreased the frequency of exacerbations *versus* placebo (-43% for moderate exacerbations, -17% for severe exacerbations, 25% reduction altogether), salmeterol alone (-12%), and fluticasone alone (-9%), and improved quality of life [1, 38]. The salmeterol-fluticasone combination did not provide a statistically significant effect on survival in the 3-yr TORCH study, which suggested a possible effect on FEV_1 rate of decline [1, 2]. Such an effect was not found in studies assessing the effect of inhaled corticosteroids alone, especially in milder COPD [39–41].

TABLE 2 Biological mechanisms accounting for the possible reduced sensitivity to corticosteroids in chronic obstructive pulmonary disease

Inflammation type
Implication of neutrophils
Signalling pathways
Excessive activation of transcription factors: nuclear factor-κB and activator protein-1
Increase in mitogen-activated protein kinase activity
Cooperation
Impairment of β2-adrenoreceptor function
Imbalance in corticosteroid receptors (decreased α/β ratio)
Raised histone acetylation
Reduced histone-deacetylase expression
Inflammation and oxidative stress consequences

It has also been suggested that budesonide added to β2-agonists (formoterol) improves exercise tolerance [42]. However, the relevance of additional clinical effects provided by inhaled corticosteroids when added to long-acting β2-agonists has been questioned [43]. In addition, although combinations of inhaled corticosteroids and long-acting bronchodilators may not be useful in all patients with severe COPD and exacerbations, available studies did not succeed in identifying a more selected subgroup of patients with clinically more relevant response [1]. Therefore, research aimed at developing other approaches to fight the inflammatory mechanisms involved in COPD is warranted.

Almost every year, reviews are published on treatment perspectives in COPD. Several classifications of lines of research seem to emerge, for example, according to whether the prime target is inflammation (cytokines, chemokines and cell adhesion molecules), protease/antiprotease or oxidant/antioxidant balance, tissue repair (growth factors, retinoids and stem cells) or mucus hypersecretion.

Airway mucus hypersecretion in COPD has been linked by pathological studies to hyperplasia of the mucin-producing proximal, and to a lesser extent to distal, bronchial epithelial goblet cells. Treatments targeting mucus hypersecretion can be classified into three types, according to whether they reduce mucin synthesis, reduce mucin secretion (*e.g.* antiproteases) or increase mucociliary clearance [44]. None of the available products targeting mucin secretion or synthesis has shown clinical efficacy. Molecules targeting mucin gel include *N*-acetylcysteine (NAC) and its derivatives (carbocysteine, erdosteine and diacetylcysteine), recombinant surfactant and ambroxol. Only cysteines have undergone methodologically satisfactory clinical trials in COPD, and their impact on natural history remains controversial. The direct impact of NAC on mucin gel is highly uncertain: its potential effects may be related to its antioxidant activity [45]. A recent meta-analysis suggested that prolonged NAC treatment reduces COPD exacerbations, although this benefit was attenuated by concomitant inhaled corticosteroids [46].

Alveolar and bronchial elastic fibre degradation is a fundamental feature of COPD pathology, resulting from protease/antiprotease imbalance characterised by increased production of elastolytic enzymes (*e.g.* neutrophil elastase, matrix metalloproteinases (MMP)-9 and MMP-12), neutrophils and macrophages and/or to antiprotease deficiency (*e.g.* α_1-antitrypsin deficiency) [47]. Proteases also play a role in bronchial remodelling and mucus secretion. Among the elastolytic enzymes, MMP-12 would seem to play a prime role [48, 49]: its potential importance in COPD pathophysiology was recently confirmed in a genetic study in >8,700 patients with asthma or COPD [50]. Numerous serine-protease (*e.g.* neutrophil elastase) or matrix MMP inhibitors are under development for cancer or sepsis treatment, but none have yet shown clinical efficacy in COPD [51]. Low-dose erythromycin administered over a period of 1 year reduced COPD exacerbation frequency *versus* placebo [52]; this clinical effect may partly come from an antiprotease effect [51].

Macrophages and neutrophils secrete many mediators implicated in COPD, notably serine-proteases and MMPs, which are directly responsible for lung parenchymal degradation. Inflammatory cell recruitment is mediated by leukotriene B_4 and by small peptides known as chemokines, which act by stimulating membrane receptors coupled to G proteins [53, 54]. More than 50 chemokines, classified as C, CC, CXC and CX3C, activate more than 20 known membrane receptors [55]; some activate a single type of receptor, while others can activate several. Receptor activation stimulates the signal transduction pathways underlying chemotaxis and also proliferation, differentiation and survival of inflammatory cells. The development of chemokine receptor antagonists would thus logically be relevant to reduce COPD inflammation [56, 57] by limiting the recruitment of inflammatory cells (in particular neutrophils) [57–59].

Theophylline has been shown *in vitro* to increase HDAC activity and response to corticosteroids [60]. Recently, FORD *et al*. [61] randomly allocated 30 patients to treatment by either: 1) oral placebo + inhaled placebo followed by oral low-dose theophylline (250 mg *b.i.d.*) + inhaled placebo (4 weeks each, separated by a 2-week wash-out period), or 2) oral placebo + inhaled fluticasone (500 μg *b.i.d.*) followed by oral theophylline + inhaled fluticasone, with a 2-week open-label extension of the latter study arm in seven subjects. Theophylline plus fluticasone had greater effects on indices of airflow obstruction than theophylline alone, and in the open-label study extension theophylline added to fluticasone increased HDAC activity in peripheral blood monocytes. There was no difference between theophylline plus fluticasone and fluticasone alone in indices of airway inflammation [61]. Thus, *in vivo* evidence of a clinically relevant potentiation of the anti-inflammatory effects of fluticasone by theophylline remains limited.

Phosphodiesterase (PDE)4 is expressed in most inflammatory and resident cells in the lungs. In COPD, the anti-inflammatory action of PDE-4 inhibitors has been explored in induced sputum: although it did not affect the percentage of inflammatory cells in induced sputum, treatment with PDE-4 inhibitor reduced the number of total cells, neutrophils and eosinophils, and the concentration of some inflammatory mediators in the sputum (IL-8, eosinophil cationic protein and neutrophil elastase) and in the serum (TNF-α) [62]. In a biopsy study, a PDE-4 inhibitor reduced CD8+ and CD68+ (macrophages) cells in bronchial biopsies of COPD patients [63]. Recently, four phase-III clinical trials assessed the effect of PDE-4 inhibitor alone or in association with long-term bronchodilators *versus* placebo, or in association with a long-term bronchodilator *versus* the bronchodilator alone: the results were consistent throughout the studies, with a reduction of some 17% (nearly 21% in patients with concomitant treatment with a long-acting β2-agonists) in moderate-to-severe exacerbation rates, which is clinically relevant in the studied population [64, 65].

Macrolides have not only antimicrobial but also immunomodulatory/anti-inflammatory effects; for instance, they decrease neutrophil activity and oxidant production and modulate cytokine production by airway epithelial cells [66]. Some studies suggested an effect of erythromycin on the frequency of exacerbations or common colds in patients with COPD [67]. Recently, results of a large 1-yr study with azithromycin (250 mg per day) were reported: this macrolide reduced exacerbation frequency by 28% and improved quality of life [68]. Such results are undoubtedly encouraging, although azithromycin treatment was also more frequently associated with hearing impairment.

Statins also have anti-inflammatory effects. They reduce both the expression of surface adhesion molecules on endothelial cells, macrophages or eosinophils and of chemokine receptors, thereby reducing recruitment and migration of inflammatory cells such as neutrophils. Statins also reduce production of pro-inflammatory cytokines. In COPD patients, statins may significantly decrease all-cause mortality and exacerbation rate [69–71]. Exacerbation severity also decreases, with a significant fall in the number of intubations and in mortality associated with or following exacerbation [72–74]. Likewise, statins impact the decline in FEV1 [75, 76]. Finally, COPD patients receiving statins show improved exercise tolerance, with improvement in performance correlating with a reduction in C-reactive protein, suggesting an effect on peripheral inflammation [77]. The clinical usefulness of these findings remains limited, however, as most findings come from nonrandomised retrospective cohort studies.

Peroxisome proliferator activated receptor (PPAR) agonists with anti-inflammatory properties are of increasing interest in the management of COPD [78, 79]. In the lungs, PPAR-γ activation inhibits pro-inflammatory cytokine secretion by macrophages and airway epithelial cells [78, 79]. It also induces T-lymphocyte apoptosis. PPAR-γ agonists also reduce airway mucus production induced by cigarette smoke. In animal models of lipopolysaccharide-induced inflammation, rosiglitazone (a PPAR-γ agonist) reduces neutrophil levels in the lung parenchyma but not in bronchoalveolar lavage [80]. The adverse cardiac effects of these molecules, however, limit their application, as COPD is frequently associated with cardiovascular comorbidity.

Several lines of research are therefore under way to develop new treatments which will act more effectively on symptoms, disability, rate of respiratory function deterioration and survival through more targeted focus on COPD-specific features of airway and systemic inflammation. One interesting aspect of current research is the growing awareness of the potential co-operation between different families of molecules.

CONCLUSION

Research into COPD inflammation is promising. Some lines of investigation will come to a dead end, while others will lead to new treatments, in some cases targeting very specific populations identified by clinical phenotyping or biomarkers. The arrival of PDE-4 inhibitors and new data on macrolides or statins as anti-inflammatory treatments in COPD represent good illustrations of how knowledge of inflammatory and remodelling phenomena finally broadened the range of treatments able to improve patients' outcomes.

The arrival of new treatments, however, should by no means overshadow the other ''unmet needs''. COPD awareness needs to be fostered in the general population and among healthcare workers, as it is a key to improving detection, especially at early stages for which treatments of proven efficacy already exist. Screening strategies should thus become more efficient. Patient education should also be developed, to improve compliance and implement sustainable lifestyle changes. Access to optimally effective care and reinforcement of progress made should be promoted by developing rehabilitation structures. Improved synergy between primary and specialised care also requires more efficient implementation before patients fall into long-term invalidity.

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