

Editorial

Reducing airways inflammation to prevent exacerbations in chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a major cause of handicap, mortality and health care expenses (1). Altered quality of life (QOL) is a hallmark of the disease, and relates mainly to dyspnoea and exacerbations: both QOL at steady-state and its rate of decline over time correlate to the frequency of acute respiratory events (2, 3). In parallel, hospitalizations for exacerbations in the most severe patients are important determinants of health care costs (4). Thus, preventing exacerbations is a major goal of care for COPD patients, both from an individual and collective point of view.

Inflammation and COPD exacerbations

In most cases, COPD occurs in smokers and ex-smokers, in whom airflow limitation is the consequence of various degrees of emphysema, chronic bronchiolitis and mucus plugging (5). These components of the disease have been linked to inflammatory and remodelling processes in the airways and lung parenchyma, involved inflammatory cells being mainly neutrophils, B and T lymphocytes and macrophages (5, 6). Airways inflammation is more intense during exacerbations, as shown by increases in the levels of (i) expression of neutrophil elastase, CXCL-5, CXCL-8 and CXCR1/2 in biopsies (7), (ii) exhaled LTB₄ and 8-isoprostane in breath condensates (8), (iii) interleukin (IL)-8 and tumour necrosis factor (TNF)- α in sputum (9).

Infections are a leading cause of exacerbations and further amplify airway inflammation (10). However, about one half of exacerbations occur in the absence of any detectable infective pathogen, which may not prevent

inflammation from increasing (11). Besides, higher levels of inflammatory markers in the airways of patients at steady-state are also associated with more frequent exacerbations (12). Studies of the East London COPD cohort even suggest the existence of a particular subgroup of COPD patients called 'frequent exacerbators', who consistently have more than 2–3 exacerbations per year (13). In these patients, QOL is more altered, forced expiratory volume at 1 s (FEV₁) declines faster and inflammation is more intense (Table 1) (3, 12, 14). Such observations do not demonstrate that increased baseline inflammation is the cause of increased exacerbation frequency: both could simply be the expression of a more severe disease. However, a causal relationship is a tempting hypothesis because inflammatory phenomena can result in (i) the release of bronchoconstricting mediators, (ii) mucus hypersecretion and (iii) tissue damage, e.g. through protease–antiprotease and oxidant–antioxidant imbalances. These events could explain (i) acute episodes of increased airway narrowing, (ii) increased susceptibility to infectious pathogens and (iii) accelerated progression of COPD.

Along this hypothesis, reducing inflammation could decrease the frequency of exacerbations and thereby improve the natural history of the disease. Several compounds might help reaching this goal.

Inhaled corticosteroids

Inhaled corticosteroids (ICS) are much less effective at decreasing airway inflammation in COPD than in asthma. Experimental studies even found some degree

Table 1. Differences between frequent and infrequent exacerbators: data from the East London COPD cohort (3, 12, 14)

	Frequent exacerbators	Infrequent exacerbators
Quality of life (SGRQ total score, mean $\pm$ SD)* (3)	64.1 $\pm$ 14.6	48.9 $\pm$ 15.6
Decline in FEV ₁ (mean rate) (14)	−40.1 ml/year	−32.1 ml/year
IL-8 levels in induced sputum (median and 95% CI) (12)	6694 (3120–11995)	1628 (607–4812)
Bacterial colonization (%) (67)	25	72†

*Saint George Respiratory Questionnaire: a higher score reflects poorer quality of life.

†Extrapolated from published figures.

COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume at 1 s; IL, interleukin.

of resistance to these drugs in COPD. At first, airways inflammation in COPD involves neutrophils, the survival of which is prolonged by corticosteroids through inhibition of apoptosis (15). Secondly, the oxidative stress, which characterizes COPD, reduces the activity of histone deacetylase, a nuclear enzyme that helps the inhibition of inflammatory gene transcription by glucocorticoids (16). Accordingly, several studies found no or little effect of inhaled or oral glucocorticoids on the inflammatory cell, cytokine and protease–antiprotease profile in patients with COPD, and macrophage response to glucocorticoids is reduced in smokers (17, 18). However, other researchers found some effects of glucocorticoids on sputum neutrophils and bronchial lymphocytes and mast cells in COPD, suggesting that resistance to glucocorticoids is not absolute and may vary between patients (19–21). This could explain the reduction of exacerbations in some glucocorticoid-treated patients (22–32) (Table 2).

In addition, some data suggest a potential for molecular cooperation between corticosteroids and other compounds such as theophylline, which restores histone deacetylase activity (33). However, despite other anti-inflammatory properties in COPD (34), a preventive effect of theophylline on exacerbations remains to be demonstrated in adequately designed trials.

Antioxidants, mucolytics, immunomodulating agents and antibiotics

Other pharmacological compounds with anti-inflammatory properties, namely mucolytic and immunomodulating agents or macrolides, may reduce the frequency of exacerbations.

Trials assessing the efficacy of mucolytic agents have been included in two recent meta-analysis: one included 23 trials on various mucolytic agents (treatment duration: 2–24 months, ≥ 6 months in 15 studies) and demonstrated a 29% reduction in the number of exacerbations with these agents (1.9 exacerbations per patient-year vs 2.7 exacerbations per patient-year in the control group) (35). Nine trials on the effect of *N*-acetylcysteine (NAC) were included in the other (treatment duration: 12–24 weeks, ≥ 20 weeks in eight studies): NAC increased the number of patients who had no exacerbations (relative benefit: 1.56, number needed to treat to gain one patient with no exacerbation: 5.8) (36). However, most of these studies addressed exacerbations of chronic bronchitis and not COPD, and a large long-term trial in 523 patients followed for 3 years did not confirm the effect of NAC on exacerbation rate, except maybe in patients with no inhaled corticosteroids, according to a prespecified subgroup analysis (37). The mechanisms by which mucolytic

Table 2. Preventive effect of inhaled corticosteroids on COPD exacerbations in placebo-controlled trials with a treatment duration of at least 12 months

Reference	N	Duration (months)	Mean FEV ₁ (% predicted)	ICS	Result (effect on exacerbation rate): active treatment vs placebo unless otherwise indicated
(22)	28	12	70 (rapid decline)	BDP 400 μ g bid	NS
(23)	274	30	64	BDP 200 μ g qid	Withdrawals mainly due to exacerbations: 0.25/patient/year vs 0.72/patient/year ($P < 0.001$)
(24)	58	24	45	BUD 800 μ g bid	NS
(25)	98	24	39	BDP 750–1000 μ g bid	NS
(26)	290	36	77	BUD 600 μ g bid then 400 μ g bid	NS
(27)	1277	36	77	BUD 400 μ g bid	NS (serious respiratory adverse events)
(28)	751	36	50	FP 500 μ g bid	Exacerbation rate: 0.99/patient/year vs 1.32/patient/year
(29)	1116	36	64	TA 600 μ g bid	Visits due to respiratory illnesses: 1.2/100 person-years vs 2.1/100 person-years
(30)*	1465	12	44	FP 500 μ g bid	34% reduction
(31)*	1022	12	36	BUD 400 μ g bid	NS
(32)*	812	12	36	BUD 400 μ g bid	41% reduction of mild exacerbations; 29% reduction of corticosteroid-treated exacerbations

BDP, beclomethasone dipropionate; BUD, budesonide; FP, fluticasone propionate; TA, triamcinolone acetonide; FEV₁, forced expiratory volume at 1 s; COPD, chronic obstructive pulmonary disease.

*Studies designed to assess the effect of a combination of an inhaled corticosteroid with a long-acting β_2 -agonist. Results are shown vs placebo. Only significant results ($P < 0.05$) are shown.

agents might prevent exacerbations are not fully elucidated but seem to be mediated by antioxidant effects: for instance, NAC reduces oxidative stress in COPD (38, 39) and is both a glutathione precursor and a thiol donor (35). Reduction of bacterial adherence or improvement in mucociliary clearance could also help reducing the frequency of exacerbations, but the link between these effects and exacerbation rate remains to be verified (38).

The effect of oral purified bacterial extracts on exacerbations has been studied in three 6-month trials, one of which was of poor quality. A meta-analysis of these trials failed to demonstrate a significant reduction in exacerbation rate (40). In addition, the influence of bacterial extracts on airway inflammation is unknown, although inflammatory processes could theoretically be decreased if infections are prevented.

Macrolides appear to have some anti-inflammatory properties: for instance, erythromycin decreases *Haemophilus influenzae* endotoxin-induced release of IL-6, IL-8 and intracellular adhesion molecule (sICAM)-1 in epithelial cells *in vitro*. Similarly, clarithromycin mildly reduces neutrophil differential count and chemotaxis while having debated effects on IL-8 and TNF- α levels in induced sputum *in vivo* (41, 42). A 1-year open trial in 109 patients indeed found an efficacy of long-term low-dose erythromycin in the prevention of common cold and exacerbations of COPD, with relative risks of developing these events in the control group of 9.26 for common colds [95% confidence interval (CI): 3.92–31.74] and 4.71 for COPD exacerbations (95% CI: 1.53–14.5) (43). This result remains to be confirmed in other studies, and a 3-month treatment with oral clarithromycin once daily did not reduce exacerbation rate in 67 patients with stable COPD (44).

Bronchodilators

An efficacy of bronchodilators (alone or associated with inhaled corticosteroids) on exacerbation rate has been demonstrated in some but not all high-quality trials (30–32, 45–47) (Table 3). The possible pathways involved in this effect remain unknown. One mechanism may be an

improvement in mucociliary clearance. However, a recent study of tiotropium compared with placebo during 3 weeks in 34 subjects did not find any short-term change in that variable, as measured by a radioaerosol technique (48). Improvement of baseline airway calibre and/or reduction in the level of bronchial responsiveness may also reduce the risk of exacerbation, but the possible role of these mechanisms remains putative (49).

Another hypothesis relies on anti-inflammatory effects of bronchodilators, which could help preventing exacerbations. Such effects have been studied for both β 2-agonists and anticholinergic agents.

β 2-Agonists

β 2-Adrenergic receptors are expressed in virtually all types of inflammatory cells, although their level of expression varies markedly from one to another. Among cells which are known to play a role in COPD, expression of these receptors has been found to be high in monocytes but much lower in macrophages, T lymphocytes or neutrophils. As a consequence, β 2 agonists inhibit the release of cytokines (TNF- α , IL-8) from monocytes, superoxide and thromboxane from alveolar macrophages, superoxide, myeloperoxidase and IL-8 from neutrophils (50). Effects of β 2-agonists on neutrophil adhesion and chemotaxis have also been demonstrated. Involved pathways include the enhanced production of cyclic AMP (cAMP) by Gs-coupled adenylyl cyclase and subsequently the activation of cAMP-dependent protein kinase A (PKA) and inhibition of mitogen-activated protein kinases (MAPK) and, thereby, protein kinase C (51). In parallel, β 2-agonists can also stimulate some MAPK pathways (namely the extracellular signal-regulated kinase – ERK–MAPK pathway) through coupling to Gi subunits. However, it must be emphasized that these data from *in vitro* studies did not prove to have significant consequences *in vivo*.

Maybe more importantly, β 2-agonists appear to enhance several effects of glucocorticoids including suppression of nuclear factor- κ B (NF- κ B) activity and inhibition of the release of proinflammatory cytokines (51, 52). These effects are associated with an increase in

Table 3. Preventive effect of bronchodilators on COPD exacerbations in placebo-controlled trials with a treatment duration of at least 12 months

Reference	N	Duration (months)	Mean FEV ₁ (% predicted)	Bronchodilator	Result (effect on exacerbation rate): active treatment vs placebo unless otherwise indicated
(45)	18	12	49	SALM 50 μ g bid	NS
(30)*	1465	12	44	SALM 50 μ g bid	29% reduction
(31)*	1022	12	36	FORM 12 μ g bid	NS
(32)*	812	12	36	FORM 12 μ g bid	15% reduction of mild exacerbations; NS for corticosteroid-treated exacerbations
(46)	921	12	38	TIO 18 μ g once daily	Exacerbation rate: 0.76/patient/year vs 0.95/patient/year
(47)	1010	12	48	TIO 18 μ g once daily	Exacerbation rate: 1.06/patient/year vs 1.64/patient/year

SALM, salmeterol; FORM, formoterol; TIO, tiotropium; IPRA, ipratropium bromide; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume at 1 s.

*Studies designed to assess the effect of a combination of an inhaled corticosteroid with a long-acting β 2-agonist. Results are shown vs placebo. Only significant results ($P < 0.05$) are shown.

Table 4. Preventive effect of inhaled corticosteroids combined with LABA on COPD exacerbations in placebo-controlled trials with a treatment duration of at least 12 months

Reference	N	Duration (months)	Mean FEV ₁ (% predicted)	ICS and LABA	Result (effect on exacerbation rate)
(45)	18 (pilot study)	12	49	FP/SALM 500/50 µg bid	Significant decrease, from 3.5 to 1.2 exacerbation/patient/year (mean values) with combination treatment. NS with SALM alone and placebo.
(30)	1465	12	44	FP/SALM 500/50 µg bid	34% reduction
(31)	1022	12	36	BUD/FORM 400/12 µg bid	24% reduction
(32)	812	12	36	BUD/FORM 400/12 µg bid	62% reduction of mild exacerbations; 31% reduction of corticosteroid-treated exacerbations

BUD, budesonide; FP, fluticasone propionate; SALM, salmeterol; FORM, formoterol; COPD, chronic obstructive pulmonary disease; LABA, long-acting β 2-agonists; FEV₁, forced expiratory volume at 1 s.

Only significant results ($P < 0.05$) are shown.

the nuclear translocation of the glucocorticoid receptor (GR) and in its binding to glucocorticoid-responsive elements. Phosphorylation of GR and GR-associated factors through β 2-responsive PKA and MAPK pathways is involved in this phenomenon, and also results in enhanced ability of GR to alter NF- κ B transactivation. Molecular facilitation of the anti-inflammatory effects of glucocorticoids by β 2-agonists may help explaining the additive effects of these two classes of agents on exacerbation rate in clinical trials (30–32, 45) (Table 4).

Anticholinergic agents

In this issue of Allergy, Profita et al. show that acetylcholine (Ach) increases neutrophil chemotactic activity and production of leukotriene B4 (LTB4) by sputum cells of COPD patients (53). These results are in accordance with previous studies in animal models, which found Ach-induced release of neutrophil, monocyte and eosinophil chemotactic activity from airway epithelial cells and alveolar macrophages (54–56). Profita et al. (53) also demonstrate that the expression of muscarinic M3 receptors is increased in sputum cells of patients with COPD, while that of M2 receptors is decreased. This is in apparent contradiction with other data showing normal function of lung neuronal M2 receptor in stable COPD patients (57). However, expression and function of neuronal and non-neuronal muscarinic receptors could be under the influence of different regulatory mechanisms (58). Finally, results in monocytes from healthy donors suggest the implication of ERK1/2 pathways in Ach-induced LTB4 release (53). In the future, it may be useful to expand this study by measuring the effect of Ach on the release of other mediators by sputum cells (e.g. IL-8) and on the global chemotactic activity of sputum. The involvement of ERK1/2 pathway also has to be assessed in sputum cells.

Nevertheless, these data already suggest some contribution of the cholinergic system to the airway inflammation which characterizes COPD. This is of particular interest when considering the potential role of non-neuronal Ach. Indeed, human airway epithelial cells

and macrophages are able to synthesize Ach (59) and both nicotinic and muscarinic Ach receptors and cholinesterase are widely expressed on non-neuronal cells including epithelial and immune and inflammatory cells. Thus, the non-neuronal cholinergic system can regulate several cell functions such as secretion, ciliary activity, proliferation and differentiation, cell–cell communication and adhesion, production of cytokines, mediators, etc. This may help explaining how tiotropium bromide, an anticholinergic agent, prevents allergen-induced smooth muscle mitogenic response in guinea-pigs (60).

However, the role of the cholinergic system in the airways of patients with COPD is probably more complex because the cholinergic stimulation also exerts anti-inflammatory effects, especially through α 7 subunit-containing nicotinic receptors; these effects include inhibition of endothelial cell activation, cytokine release and leucocyte recruitment (61, 62). Thus, exposure to Ach may result in differential effects depending on the dominant type of Ach receptor which is stimulated. The study by Profita et al. (53) suggests that the dominant effect of anticholinergic agents *in vivo* could be anti-inflammatory, but this has to be studied further.

In conclusion, β 2-agonist or anticholinergic bronchodilators appear to have some preventive effects on COPD exacerbations, when used alone or in combination with inhaled corticosteroids. Because these agents have some anti-inflammatory properties while exacerbations are associated with increased airway inflammation, it is tempting to hypothesize that prevention of exacerbations is a consequence of decreased inflammation. However, direct evidence of the causal link between these observations is still lacking.

If control of inflammatory phenomena reduces the frequency or severity of acute episodes, new treatments may have interesting potential: first clinical results with phosphodiesterase inhibitors are encouraging (63), although their full publication is awaited; several more targeted compounds are currently being developed, as recently reviewed (64); they include: (i) inhibitors of some cell signalling pathways involving p38 MAP kinases,

NF- κ B, phosphoinositide-3 kinase- γ , (ii) antagonists of lipid mediators (LTB₄), chemokines (IL-8, monocyte chemoattractant protein-1, growth-related oncogene- α) and cytokines (TNF- α , IL-1 β), (iii) antioxidants including inhibitors of nitric oxide synthase.

Despite all these perspectives, smoking cessation remains the best way to modify the natural history of the disease, although it does not result in disappearance of airway inflammation (65, 66).

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