Inhaled and Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease

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Systemic and local inflammation is central to the pathophysiology of chronic obstructive pulmonary disease (COPD). Increased levels of inflammation have been linked to a more progressive course in COPD and have been shown to be present during an exacerbation. Decreases in inflammatory cytokines, C-reactive protein, and inflammatory cells have been observed with corticosteroid use, suggesting a possible mechanism for a therapeutic benefit of steroids. No available data support the routine use of systemic corticosteroids in stable COPD; however, short courses during exacerbations are likely to improve length of hospitalization, lung function, and relapse rate. Inhaled corticosteroids (ICS) decrease the rate of exacerbation and may improve the response to bronchodilators and decrease dyspnea in stable COPD. No study shows that ICS reduce the loss of lung function; however, recent data suggest a possible survival benefit when combined with long-acting β agonists. There are limited data on the use of ICS in the treatment of acute exacerbations of COPD, and its role in this setting must be more clearly defined. The empiric use of systemic corticosteroids perioperatively represents another area of uncertainty. The role of pharmacogenetics in the metabolism of corticosteroids in COPD is evolving but may be partially responsible for the observed variability in patient responsiveness. The potential benefits of systemic or inhaled corticosteroid use must be weighed against the risk of known toxicities.

Keywords: steroids; emphysema; inflammation; chronic bronchitis

Chronic obstructive pulmonary disease (COPD) has been defined as airflow limitation that is not fully reversible, is progressive over time, and is associated with an abnormal inflammatory response to noxious particles or gases (1). As the pathogenesis of COPD becomes better understood, the role of past and ongoing inflammation has received increased attention. Systemic and local inflammation has been implicated in COPD, and the use of systemic and inhaled corticosteroids (ICS) has been considered critical to COPD treatment. This article reviews the current role of systemic and ICS in severe COPD treatment in stable health and during acute exacerbations.

ROLE OF INFLAMMATION IN COPD

Tissue Inflammation

Although systemic inflammation is clearly present in COPD, local inflammation within the airways and lung parenchyma is a likely starting point for the inflammatory cascade. Airway inflammation is significantly increased during exacerbations of COPD, with evidence of increased neutrophils, lymphocytes, and eosinophils seen in airways and in sputum (2–4). Histone deacetylase (HDAC) is reduced in the alveolar macrophages of cigarette smokers and inhibits the production of inflammatory cytokines in alveolar macrophages. Reduced HDAC activity and increased histone acetyltransferase correlate with increased exacerbation and COPD disease severity and are associated with corticosteroid insensitivity in these patients (5). Hogg and colleagues recently provided evidence of increasing degrees of airway infiltration with neutrophils, macrophages, CD4 cells, CD8 cells, B cells, and lymphoid aggregates containing follicles as well as airway thickening with worsening severity of COPD (6). Significant ongoing inflammation was noted even in patients who had abstained from smoking for several years, suggesting a persistent, perhaps maladaptive, response to previous injury. A more thorough review of local inflammatory mediators is shown in Table 1.

Systemic Inflammation

COPD affects more than just the lungs. Muscle wasting, cachexia, atherosclerosis, and cardiac disease have been associated with COPD. These nonpulmonary manifestations of COPD suggest a systemic disorder that is likely mediated by circulating inflammatory cells and inflammatory cytokines (Table 1).

Neutrophil activation seems to play a central role in the pathogenesis of COPD. Several recent studies have shown heightened neutrophil activation in patients with COPD compared with normal individuals. Burnett and colleagues showed that peripheral neutrophils taken from patients with stable COPD had significantly increased *in vitro* chemotactic and proteolytic activity compared with neutrophils obtained from normal individuals (26). Genetic evidence of peripheral neutrophil activation has been provided by Oudijk and colleagues, who obtained peripheral neutrophils from normal volunteers and from patients with COPD after stimulation with tumor necrosis factor-α and/or granulocyte-macrophage colony–stimulating factor. The severity of COPD as determined by the FEV_1 correlated with concentrations of IL-1β, MIP-1β, CD83, IL-1 receptor 2, and IL-1 receptor antagonist as measured by gene microarray (30). Although it seems that peripheral neutrophilic activation occurs in COPD, its clinical significance has yet to be elucidated.

Less information is available regarding the role of peripheral lymphocyte function in COPD. Increased lymphocyte apoptosis and the production of transforming growth factor-β have been shown in stimulated peripheral lymphocytes of patients with COPD (27). Increased peripheral lymphocyte activation has also been seen in COPD, as well as up-regulation of Toll-like receptor 2 (TLR-2), matrix metalloproteinase-9, IL-6, and monocyte chemoattractant protein-1 (MCP-1) from peripheral monocytes (28, 29, 31, 32).

Many circulating inflammatory mediators have been observed to be elevated in stable COPD and during exacerbations. C-reactive protein (CRP) is a known marker of systemic inflamma-

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TABLE 1. EVIDENCE OF PULMONARY AND SYSTEMIC INFLAMMATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Location	Evidence (Reference)
Lungs	Airway wall infiltration by T lymphocytes and macrophages (7–9)
	Increased cytokines such as TNF-α, IL-8 (7, 10)
	Decreased IL-10 (11)
	Increased IL-6 during exacerbations (12, 13)
	Elevated GRO-α (14)
	Reduced HDAC and increased HAT
Blood	Increased leptin (15)
	Increased levels of IL-6 and TNF-α (16–19)
	Increased CRP (20–24) and fibrinogen (12, 18, 25)
	Peripheral neutrophil activation (12, 26)
	Increased activation and apoptosis of peripheral lymphocytes (27–29)

Definition of abbreviations: CRP = C-reactive protein; GRO = growth-related oncogene; HAT = histone acetyltransferase; HDAC = histone deacetylase; TNF = tumor necrosis factor.

tion and a likely participant in the inflammatory cascade (33). CRP has been implicated as a marker of infection and cardiovascular disease; however, the relationship between CRP and COPD is less clear. Dev and colleagues first described an association between CRP and exacerbations of COPD in 50 patients admitted for exacerbations of COPD. CRP levels were significantly elevated on admission and dropped to near normal levels after treatment. Although the marked elevation in CRP was more pronounced for patients with proven bacterial infection, patients with no identified pathogen had a similar rise and fall in CRP level (34). Elevated CRP levels have also been shown in stable COPD when compared with smokers without COPD and seem to be independent of the presence of cardiovascular disease (22). Elevations in CRP in COPD have also been linked to exercise limitation, increased airflow limitation, and dyspnea (23). Last, elevations in CRP levels in patients with COPD have been shown to be a strong indicator of important clinical outcomes, including hospitalization and death (35).

Role of Corticosteroids in Inflammation

As more evidence mounts implicating inflammation in the pathogenesis and maintenance of COPD, therapeutic strategies meant to halt or reverse inflammation are desirable. The use of inhaled or systemic corticosteroids has been the cornerstone in antiinflammatory therapy in all settings of COPD. The use of steroids in COPD remains controversial because of questionable benefit and potentially significant drug toxicity. Because neutrophils, T lymphocytes, and macrophages have been implicated in the pathogenesis of COPD, investigators have sought evidence that steroids may alter the biological behavior of these cell lines and other inflammatory mediators (Table 2). The effect of steroids on neutrophils has traditionally been considered to be minimal; however, there are data indicating that steroids induce neutrophil death *in vitro* (44, 45). Additionally, decreased neutrophils and IL-8 levels in bronchoalveolar lavage samples have been demonstrated in patients with COPD who were treated with inhaled budesonide, suggesting a potential mechanism of action for steroids in this patient population (46). Biopsies of airways of smokers with COPD given inhaled fluticasone showed decreased CD8:CD4 ratios and decreased subendothelial mast cells when compared with patients receiving placebo (41). In this study, patients receiving inhaled fluticasone had fewer COPD exacerbations, suggesting that alterations in airway inflammation may have played a role in the beneficial effect of ICS (41). One plausible explanation for the therapeutic effect of corticosteroids in COPD suggests that HDAC in the presence of corticosteroids down-regulates the transcription of inflammatory cytokines (5). Clinical observations made with the use of systemic and ICS support the notion of corticosteroids exerting an inhibitory effect on inflammatory mediators. Additionally, patients with COPD in whom ICS are withdrawn show reductions in CRP level when retreated with ICS and systemic corticosteroids, whereas patients retreated with placebo do not (43).

VARIABLE RESPONSIVENESS TO CORTICOSTEROIDS

Despite large prospective trials showing modest benefits for the use of corticosteroids in COPD, there seems to be a great deal of patient-to-patient variability regarding efficacy. Pharmacogenetics provides a potential rationale for this variability. Weiss and colleagues identified a single gene that had several single nucleotide polymorphisms in adult and pediatric patients with asthma that correlated well with response to ICS (47). More recently, Ito and colleagues showed a decreased concentration of HDAC in peripheral lung tissue from patients with COPD (5). The concentration of HDAC correlated with the severity of COPD. HDAC suppresses inflammatory gene expression, thus giving rise to more robust inflammatory responses, and may be central to the pathogenesis of COPD. HDAC-2, one of

TABLE 2. BENEFICIAL EFFECTS OF SYSTEMIC AND INHALED CORTICOSTEROID THERAPY IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

	Systemic Corticosteroid (Reference)	Inhaled Corticosteroid (Reference)
Lung	Reduced MP levels in sputum (36)	Reduced oxidative stress (40)
	Decreased eosinophils in sputum (37, 38)	Reduced mast cells (41)
	May reduce basal release of GM-CSF by alveolar macrophages (39)	May down-regulate production and/or release of IL-6 and IL-8 from bronchial epithelial cells (42)
Blood		Reduced CRP levels (43)
Clinical	Improved PFTs (52), shorter hospitalization (55), and reduced rate of treatment failure (55) in acute exacerbations	Reduced bronchial hyperreactivity (65)
		Reduced exacerbations in moderate to severe COPD (59, 60, 67, 68, 72)
		Slowed rate of decline in health status and QOL (59)
		Improved pre-BD FEV_1, oxygenation, and dyspnea (61)
		Discontinuation of ICS may lead to increased exacerbation rates and worse QOL (62)
		ICS + LABAs: improved pre-BD FEV_1 (68–71)
		Improvement in cough, sputum score, and reduced use of reliever medications (41)
		May reduce mortality (69, 73–80)
		May improve post-BD FEV_1 during acute exacerbations (89)

Definition of abbreviations: BD = bronchodilator; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; GM-CSF = granulocyte-macrophage colony–stimulating factor; ICS = inhaled corticosteroids; LABAs = long-acting β-agonists; MP = myeloperoxidase; PFT = pulmonary function test; QOL = quality of life.

11 HDAC isoenzymes located within the cell nucleus, is vital to the ability of corticosteroids to turn off inflammatory genes (48). Lung concentrations of HDAC-2, or perhaps polymorphisms of the genes, may confer varying degrees of steroid resistance to patients with COPD.

SYSTEMIC CORTICOSTEROIDS

Stable COPD

As the pathogenesis of COPD has become better understood, it has become clear that systemic inflammation may be responsible for many of the symptoms and the reduction in quality of life (QOL). It therefore seems reasonable that the chronic use of systemic corticosteroids to reduce inflammation may be beneficial in COPD. However, no study has shown a significant long-term benefit of systemic corticosteroids in stable COPD (49). In fact, there is a suggestion that the use of systemic steroids in patients over the age of 65 with stable COPD may increase mortality (50). Additionally, chronic use of systemic corticosteroids is associated with significant toxicity, including hyperglycemia, myopathy, hypertension, and osteoporosis. Systemic steroids may be safely weaned from chronic users with COPD without adversely affecting lung function, dyspnea, and exacerbation rate. The most notable physiological change in patients weaned from corticosteroids was a significant loss of weight (51).

Exacerbations of COPD

Systemic corticosteroids have been shown to improve pulmonary function, shorten hospitalizations, improve dyspnea, and decrease relapse rate in the treatment of exacerbations (52–58). Three prospective, randomized controlled trials have looked at the use of systemic steroids in the treatment of inpatients with COPD exacerbations (52, 55, 56). Albert and colleagues randomly assigned patients admitted for COPD exacerbations to 0.5 mg/kg of intravenous methylprednisolone every 6 hours for 72 hours or to placebo (52). There was a significant improvement in pre- and post-bronchodilator FEV_1 in those treated with methylprednisolone. In another large trial comparing placebo with 2 and 8 weeks of systemic corticosteroids, the rate of treatment failure (defined as death from any cause, need for intubation and mechanical ventilation, readmission to the hospital for COPD, or intensification of drug therapy) was found to be significantly higher in the placebo group at 30 and 90 days (55). Additionally, patients in the corticosteroid arms showed improvements in FEV_1 for the first 3 days and had shorter lengths of stay. There were no significant differences between 2 and 8 weeks of corticosteroids. Patients in the steroid groups had an increased incidence of hyperglycemia compared with those in the placebo group.

INHALED CORTICOSTEROIDS

Stable COPD

The use of ICS in the treatment of stable COPD has been in clinical practice for decades; however, the precise role of ICS remains controversial. There have been many prospective, placebo-controlled trials examining the benefit of ICS in stable COPD (59–66). Two large early trials examining the benefits of inhaled budesonide in patients with mild airflow obstruction had similar results. Pauwels and colleagues conducted a 3-year study of 1,277 smokers with mild COPD who were given inhaled budesonide or placebo. Although there was no slowing in the rate of decline in lung function over the study period, there was an initial significant improvement in FEV_1 and a slowing of the progression of disease over the initial 6 months of the study when compared with placebo (64). In a similar study, Vestbo and colleagues prospectively followed 290 patients with mild to moderate COPD and found no change in the rate of decline of FEV_1. There was no decrease in the rate of exacerbation with ICS in this patient population (63). The Lung Health Study in many ways mirrored the findings previously reported on the absence of benefit of ICS on decline in lung function; however, there were positive secondary benefits, including improved symptoms, decreased physician visits, and less airway hyperreactivity (65). Improved secondary endpoints in this study may have been a result of the inclusion of patients with more severe disease.

Evidence supporting the use of ICS in patients with severe COPD has been provided by the ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) trial in which 751 patients with COPD were randomized to receive inhaled fluticasone twice daily or placebo over a 3-year period (59). Although there was no difference between groups in the rate of decline in lung function, the group treated with ICS had significant reductions in rate of exacerbation, improved response to bronchodilator therapy, and improved QOL as measured by the St. George's Respiratory Questionnaire. The ISOLDE trial did not examine treatment effect by severity of disease. In a follow-up to the ISOLDE trial, Jones and colleagues looked at the efficacy of inhaled fluticasone in reducing the rate of exacerbations in patients with moderate/severe versus mild COPD as determined by an FEV_1 of less than 50% predicted or above 50% predicted, respectively. Improvements in the rate of exacerbation was limited to patients with severe disease; however, when patients who had at least one exacerbation were examined, both the mild and severe groups showed decreased rates of exacerbation with the addition of ICS (60), Further support for the role of ICS in COPD comes from the COPE study in which patients were treated with high-dose inhaled fluticasone for 4 months. The ICS was discontinued in half of the patients, who then received placebo. Patients discontinuing fluticasone had increased rates of exacerbation and worse QOL as measured by the St. George's Respiratory Questionnaire (62).

With the recent availability of combined long-acting β-agonists (LABAs) and ICS, there have been a number of trials examining their efficacy in COPD (67–72). Two similar 24-week trials of combined fluticasone and salmeterol have shown improved lung function and measures of dyspnea when compared with placebo or either individual component, which were sustained throughout the study period (69, 70). In a 12-month study, Calverley and colleagues evaluated 1,465 patients with moderate to severe COPD and examined the effect of combined fluticasone and salmeterol on lung function over 1 year (71). Pretreatment FEV_1 improved significantly when compared with placebo or with ICS or LABAs given alone. Combined treatment improved QOL and decreased the rate of exacerbation, particularly in patients with an FEV_1 of less than 50% predicted (71). Patients with severe COPD may show particular benefit to combined ICS and LABAs as when compared with LABAs alone because patients with an FEV_1 of less than 50% predicted had a 35% reduction in moderate and severe COPD exacerbations over a 44-week study period (72). A Cochrane review of prospective, randomized controlled trials examining the role of combined LABAs and ICS revealed an overall improvement in pre-dose FEV_1 in patients receiving both LABAs and ICS compared with placebo or with LABAs or ICS alone. No differences in rates of exacerbation were observed with combined LABAs and ICS compared with ICS alone (73). There were conflicting results regarding QOL measures, although fluticasone/salmeterol and budesonide/formoterol were superior to placebo.

Until recently, no large, prospective, controlled trials had shown that use of inhaled or systemic corticosteroids altered the

natural history of COPD or affected survival (49, 65)/ Several recent observational studies have provided conflicting results with regards to survival (50, 74–80). The TORCH (Towards a Revolution in COPD Health) trial randomized approximately 6,000 patients with COPD to combined fluticasone/salmeterol, fluticasone alone, salmeterol alone, or placebo and treated them for a 3-year period. The primary endpoint was death from any cause. There was a 17.5% risk reduction for death in the combined group compared with placebo, which nearly ($P = 0.052$) met statistical significance (68). In addition to a reduction in all-cause mortality, there were statistically significant improvements in yearly exacerbation rate ($P < 0.001$) and pulmonary function in the combined group (62-ml decrement over 3 yr in placebo group vs. 29-ml increase in the combined group; $P < 0.001$). There was a significant increase in the rate of pneumonia in the two corticosteroid arms when compared with placebo (19.6 and 18.3% vs. 12.3%, respectively; $P < 0.001$). This increase in pneumonia rate did not translate into increased mortality. Another recent publication by Aaron and colleagues followed 449 patients with moderate to severe COPD who were randomized to 1 year of inhaled tiotropium, tiotropium plus salmeterol, or tiotropium plus salmeterol and fluticasone (81). There were no statistically significant differences in the three groups regarding having at least one exacerbation during a year, but the fluticasone-containing arm did show improvements in lung function ($P = 0.04$), QOL ($P = 0.01$), and a reduction in hospitalizations for COPD exacerbations ($P < 0.01$). In contrast to the TORCH trial, no increase in rate of pneumonia was observed for the corticosteroid-containing arm; in fact, the percentage of patients reporting pneumonia over the course of the 1-year study was only 0.7%.

Although the clinical observation that an additive benefit of ICS and LABAs for patients with COPD exists, the mechanism of this finding is less clear. Some have proposed that the addition of an LABA to ICS promotes bronchodilation and thus improved delivery of drug to distal airways. On a molecular level, steroids may have a beneficial effect on β_2-adrenoceptors, including receptor up-regulation and a reduction in tachyphylaxis, thus maximizing the effect of β-agonists (82–84). Alternatively, β-agonists have been shown to augment glucocorticoid receptor function (85–88).

ICS in the Treatment of Acute Exacerbations of COPD

The possibility of using ICS rather than systemic corticosteroids for acute exacerbations of COPD is theoretically attractive because patients may be spared the toxicity associated with systemic corticosteroids. Maltais and colleagues reported successful use of nebulized budesonide in treating acute exacerbations of COPD (89). Patients were randomized to 2 mg nebulized budesonide every 6 hours, 30 mg of prednisolone every 12 hours, or placebo for 72 hours. The budesonide and prednisolone groups had statistically significant improvements in postbronchodilator FEV_1 when compared with the placebo group, but no differences were noted between the budesonide and prednisolone groups. A significantly increased number of patients in the prednisolone groups became hyperglycemic.

PERIOPERATIVE USE OF CORTICOSTEROIDS

There are scant prospective, randomized data examining the use of systemic corticosteroids in the perioperative management of the patient with COPD. Bingol and colleagues studied 40 patients with moderate COPD who underwent coronary artery bypass surgery (90). Half of the patients were randomized to receive 20 mg of prednisolone 10 days before surgery and then continued with prednisolone until the day of surgery, after which the dose was halved every third day; the other 20 patients received placebo. The steroid group had a significant improvement in FEV_1 on the day of surgery and just before discharge; however, by 3 months there was no difference in lung function. Patients receiving steroids had shorter duration of mechanical ventilation, shorter ICU stays, and shorter overall hospital days. Although this study was limited in size, it provides a basis for a larger trial.

STEROID TOXICITY

ICS

The rationale for the use of ICS is multifactorial. It allows delivery of a drug directly to the target organ and the ability to use lower cumulative doses of corticosteroid and to avoid systemic absorption. Although a complete absence of systemic absorption of ICS would be ideal, this is not the case. Because of first-pass metabolism of the liver, virtually none of the ICS typically used for the treatment of COPD, fluticasone proprionate and budesonide, are absorbed through the gastrointestinal tract (91). Therefore, the vast majority of systemically absorbed corticosteroid occurs through the lungs. In the case of fluticasone, less systemic absorption occurs in patients with diseased lung than in patients with normal lung function (91). Despite the theoretical benefit of lower overall systemic corticosteroid levels, there are documented adverse biological effects of ICS use, including adrenal suppression, loss of bone mass density, and increased risk of fracture, glaucoma, and skin bruising (91). The TORCH trial showed no increase in the rate of fractures in either of the groups receiving ICS (68).

Systemic Corticosteroids

The toxicities associated with short- and long-term use of systemic corticosteroids are extensive and have been well described previously (92). Regarding treatment of COPD, toxicities seem to be linked to cumulative dose and duration of therapy. Patients with stable COPD treated with systemic corticosteroids have been noted to have increased risk of glucose intolerance, decreased serum levels of osteocalcin, and increased risk of adrenal insufficiency (49). In addition, the degree of respiratory and peripheral muscle weakness has been shown to correlate with dose and duration of systemic steroid use in chronic treatment of COPD (93). Courses of systemic steroids for exacerbations have been associated with hyperglycemia, weight gain, insomnia, anxiety, and depression (58).

Recommendations

Existing evidence indicates that short courses (2 wk or less) of systemic corticosteroids are effective in improving lung function and reducing morbidity associated with COPD exacerbations in patients with moderate to severe COPD (55, 56). The use of systemic steroids for stable COPD is not recommended. Any potential benefit with systemic corticosteroids should be weighed against their potential toxicities on an individual basis. Based on the available literature, it is reasonable to initiate stable patients with moderate to severe COPD on an ICS/LABA combination regimen or ICS alone with the goal of improving lung function, reducing the frequency of exacerbations, and improving QOL. Results from the TORCH trial are promising, with hopes of improving survival with the use of combined LABA and ICS, but this needs to be further studied in light of a potential for increasing rates of pneumonia. In addition, the combination of tiotropium, LABAs, and ICS may have some benefit but further studies are needed. This recommendation is in line with the current recommendations of the Global Initiative for Chronic Obstructive Lung Disease (1).

CONCLUSIONS

COPD is a systemic disorder that carries significant morbidity. Local and systemic inflammation seem to be central to its pathogenesis and will likely be targets of future therapeutic modalities aimed at ameliorating symptoms and perhaps altering the natural history of the disease. There is a growing body of data suggesting that corticosteroids can reduce systemic and local inflammation providing a plausible mechanism for clinical benefit in COPD. Ample evidence exists to recommend short courses of systemic corticosteroids for COPD exacerbations. The use of ICS in stable COPD improves lung function, decreases rates of exacerbation, and seems to improve survival when combined with LABAs but must be weighed against the potential for increased vulnerability to pneumonia. Although the data are limited, there may be a role for perioperative use of systemic corticosteroids in COPD, although more investigation is warranted. As with all medical interventions for COPD, a careful examination of risk–benefit ratio must be partaken, particularly in light of the significant adverse effects associated with corticosteroid usage.

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