Corticosteroid Therapy and Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease is characterized in part by a chronic inflammatory state in the airways (largely from chronic noxious stimuli such as tobacco smoke), punctuated with acute inflammatory exacerbations, which are often infectious. Although pathologically and biochemically different from the inflammation of asthma, the chronic inflammation of chronic obstructive pulmonary disease, especially in subgroups with asthma-like features and especially during exacerbations, might be expected to respond to corticosteroid therapy, as does asthma. Complications from long-term corticosteroid use are important, but they appear less when the corticosteroid is given via the inhaled route. Clinical evidence is particularly strong supporting the use of inhaled corticosteroids to prevent exacerbations and oral corticosteroids to reduce the duration and impact of exacerbations. *Key words: chronic obstructive pulmonary disease, exacerbation, corticosteroids*. [Respir Care 2006;51(3):289–296. © 2006 Daedalus Enterprises]

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disorder characterized in part by chronic inflammation of the airways of the lungs.[1–3] This chronic inflammation is complicated by episodes of acute inflammation (often from infection), termed acute exacerbations of COPD (AECOPD).[4] The chronic inflammation of COPD may have different degrees of involvement in different lung regions in different patients. For example, if the disease is more prominent in the proximal airways, symptoms of cough and phlegm predominate (chronic bronchitis). In contrast, if the disease is more prominent in the distal small-airway regions of the lung, there may be concomitant alveolar destruction (emphysema) and the sensation of dyspnea may predominate. The most common cause of COPD is tobacco smoke exposure, although a small percentage of COPD patients are never-smokers and are thought to develop chronic airway inflammation and alveolar destruction from genetically determined impaired airway defenses (eg, alpha-1 antitrypsin deficiency).[1,2]

The prevalence of COPD in the United States has been estimated at between 5 and 10 million people.[1,2] The reason for this estimate variability is that many patients with subclinical COPD have simply not yet been diagnosed, since the development of clinically important symptoms usually requires substantial loss (ie, $>$ 30–50%) of lung function. The natural history of COPD depends heavily upon the continued exposure to tobacco smoke. Specifically, in COPD patients who continue to smoke, the rate of decline in forced expiratory volume in the first second (FEV_1) is several times faster than in those who quit smoking and those without COPD.[5] On average, COPD patients experience 2 AECOPDs each year.[6] The lung recovery from these exacerbations can take several weeks, but it

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may take many more months for the patient to return to baseline lung function.[4,7] Indeed, a patient with an AECOPD that requires mechanical ventilation may never return to baseline lung function.

There are no medications that reverse the natural history of COPD, and COPD therapy is generally aimed at alleviating symptoms, improving function, and reducing exacerbations and hospitalizations.[3,8,9] Although the inhaled β agonists and anticholinergics are the mainstay of a COPD treatment regimen, corticosteroids can also play an important role.[10] Interestingly, the pattern of corticosteroid use in COPD has changed over the last half century. Long-term oral corticosteroid (OCS) use was a fairly common practice in the mid-to-late 20th century, but it is estimated that now only 4–10% are considered truly *oral-steroid-dependent*.[6,11] In place of OCS has been an increasing use of inhaled corticosteroids (ICS), to improve symptoms and reduce exacerbations (approaching 65% of the COPD population in some studies[12]). A growing evidence base supports the use of short courses of OCS therapy during AECOPDs to shorten the duration and improve the outcomes of the episode.[10] In the remainder of this paper I review the rationale for corticosteroids, the potential problems with corticosteroids, the evidence base supporting the use of corticosteroids, and finally the recommendations from major organizations for how to use corticosteroids in COPD.

The Rationale for Corticosteroids in COPD

It has been known for decades that pharmacologic doses of corticosteroids reduce a variety of inflammatory processes. In the field of respiratory diseases this has been most extensively studied in asthmatic patients, in whom oral, parenteral, and inhaled corticosteroids have been used for both long-term treatment and acute flares of asthma.[13] The question then becomes whether the inflammatory state present in COPD might have a similar response to corticosteroids.[14]

From a cellular and molecular perspective, the inflammation of asthma and COPD have many differences (Table 1).[15] In asthma there is an important immunologic component, with heavy involvement by eosinophils and cluster-of-differentiation (CD4) positive T lymphocytes. In contrast, COPD is a response to noxious agents (eg, tobacco smoke), a disease in which macrophages, neutrophils, and CD8-positive T lymphocytes play major roles. In asthma, important mediators include interleukins IL4, IL5, and IL13, whereas in COPD IL8 and tumor necrosis factor alpha (TNF-α) appear to be more important. In COPD there are also more reactive oxygen species. From a pathology perspective, asthma has epithelial shedding and very little fibrosis. In contrast, COPD has alveolar destruction, airway scarring, airway fibrosis, and squamous metaplasia. From these considerations then, 2 fundamental questions arise:

1. Will the COPD inflammatory process respond to corticosteroid therapy as well as does the asthma inflammatory process?
2. Alternatively, might it be only subgroups of COPD patients with asthma-like pathology patterns who would be amenable to corticosteroid therapy?

Table 1. Inflammation Characteristics in Asthma and COPD

Inflammation	Asthma	COPD
Cells	Eosinophils	Neutrophils
	CD4+ T cells	CD8+ T cells
	Macrophages + Mast cells	Macrophages +++
Mediators	Leukotriene B4, histamine	Leukotriene B4
	IL-4, IL-5, IL-13	IL-8, TNF-α
	Reactive oxygen species +	Reactive oxygen species +++
Effects	All airways	Peripheral airways
	Little fibrosis	Lung destruction
	Epithelial shedding	Fibrosis + Squamous metaplasia
Response to steroids	+++	$\pm$

CD = cluster of differentiation
IL = interleukin
TNF = tumor necrosis factor (Adapted from Reference 15.)

Although neutrophil-predominant inflammation is often less responsive to corticosteroid therapy than is eosinophil- or lymphocyte-predominant inflammation,[16] there are features of COPD inflammation that may be amenable to corticosteroid therapy. For example, corticosteroids may enhance β-agonist activity[17] and may reduce the systemic inflammatory state induced by COPD.[18,19] In addition, exhaled biomarkers of inflammation in COPD appear to be reduced by corticosteroids.[20–22] Despite these observations, many of the clinical trials described below found minimal or no corticosteroid effects on lung function. One possible explanation for this discrepancy is that the chronic inflammatory state of COPD, as well as oxidative stress from continued tobacco smoke exposure, may impair corticosteroid receptors.[14]

There are clinical data that suggest that there is an airway hyperresponsive or asthma-like inflammatory process in certain COPD subgroups.[23–25] Hyperresponsiveness in turn might suggest an active inflammatory process amenable to corticosteroid therapy.[26] For example, in 1,116 COPD patients in the Lung Health Study, methacholine responsiveness at doses < 10 mg/mL was seen in 59% of the population.[23] Similarly, in several studies up to 50% of patients with COPD had substantial FEV_1 reversibility after a β-agonist bronchodilator.[24,25] Pathology studies have

also identified that some COPD patients may have asthma-like pathology intermixed with their COPD pathology.[27–31] For example, there are subgroups who appear to have high levels of eosinophils (especially during exacerbations), and these patients seem to be particularly responsive to corticosteroids.[31,32]

Complicating this picture further are the pathological and biochemical patterns of inflammation during AECOPDs.[4,33] These episodes are often characterized by a response to either viral or bacterial pathogens that involves the influx of various inflammatory cells and mediators, and increases in airway hyperresponsiveness. These acute changes might be particularly amenable to corticosteroid therapy.

Taken together, these observations offer the possibility that corticosteroid therapy might have some impact on the chronic inflammation of COPD, but might be expected to have greater impact in COPD patients who have asthma-like features or those experiencing AECOPDs.

Corticosteroid Risks for Patients With COPD

There are a number of potential adverse effects from both short-term and long-term administration of corticosteroids in COPD.[10] ICS, by nature, generally have lower blood levels than OCS, and this may mean less adverse effects with ICS.

Suppression of the hypothalamic-pituitary-adrenal axis has long been known to be a consequence of high-dose corticosteroids.[34] A recent meta-analysis, however, indicated that ICS use causes some suppression but that the suppression appears to be of questionable clinical importance.[35] Osteoporosis and fractures are also known complications of long-term OCS use.[36] Another meta-analysis of ICS use and bone function has indeed shown some reduction in bone density, but no increase in fractures.[3] It is important to note, however, that these data are difficult to interpret in the COPD population, in whom the chronic airway inflammation and tobacco smoking are also well known risk factors for osteoporosis.[37,38] OCS have been associated with peptic ulcer disease,[39] but the effect of ICS use on ulcer disease is not known. Similarly, psychoses are associated with long-term OCS use,[40] but, again, this has not been carefully assessed in ICS usage. Infections increase with higher doses and longer duration of OCS therapy.[41] ICS therapy is associated with local infections such as candidiasis.[42] Glucose control is more difficult with OCS use in COPD.[43] One study showed that 15% of COPD patients using OCS required additional treatment for hyperglycemia, as compared to 4% in the control group.[44] Respiratory muscles are also affected by long-term OCS use,[45] but this has not been observed with ICS use. This myopathy is difficult to evaluate in COPD patients, however, because of the systemic inflammatory nature of COPD and its effects on skeletal muscle function.[46]

Prolonged OCS use is associated with skin breakdown and bruising.[47] Moreover, high-dose ICS use is associated with bruisability.[48] Finally, OCS use is associated with an increased risk of cataracts,[49] and ICS use in COPD is associated with a 3-fold higher risk for cataracts[50] and a 1.44 odds ratio for glaucoma.[51]

Taken together, these data remind us that corticosteroids pose potentially important risks to patients. This is particularly true with long-term high-dose OCS. ICS use appears to have considerably fewer adverse effects, but the effects are important and need to be considered in making the decision to give a patient corticosteroid therapy.

The Evidence Base for Clinical Efficacy of Corticosteroids in COPD

Studies of adrenocorticotropic hormone for chronic airway diseases other than asthma were first reported in the 1950s.[52,53] These studies, however, were observational in nature, had pulmonary function as the primary end point, and used only very short courses of adrenocorticotropic hormone. Moreover, the study populations were complicated by patients with sarcoid, asthma, interstitial lung disease, and other chronic lung processes.

In 1999, Callahan et al performed a meta-analysis of the trials that had been published up to that date, that used OCS therapy in COPD.[54] These studies generally evaluated short-term uses of corticosteroids (eg, $\leq$ 21 d) and the end point was almost always an increase in FEV_1. In this meta-analysis, using a 20% improvement in FEV_1 as an indication of benefit, the weighted mean effect was 10–11% (95% confidence interval 4–18%). There was a range of 0–56% responders in these studies. What this means is that only a small fraction of COPD patients would seem to have objective physiologic benefits from a short course of OCS. Unfortunately, this meta-analysis was unable to identify how these patients could be identified a priori, although it did suggest that more severe forms of COPD might be more amenable to OCS therapy.

Since that meta-analysis, a few other studies have assessed the role of OCS use in stable COPD patients.[55–57] Two studies of note compared OCS and placebo therapy in COPD patients by measuring FEV_1 response. Robertson et al found that 2 weeks of OCS (versus placebo) produced a comparable FEV_1 response of $\geq$ 20% in 30% of 83 COPD patients.[55] Weir et al studied 127 COPD patients, who were given OCS (versus ICS) for 2 weeks. Forty-two percent of those on OCS had an FEV_1 increase of $\geq$ 20%.[57] As with the Callahan meta-analysis, these studies suggest that a small but important minority of COPD patients do seem to have a response to OCS therapy. All of these studies, however, have examined only short-term physiologic effects and they offer no insight on long-term healthcare outcomes in stable COPD patients.

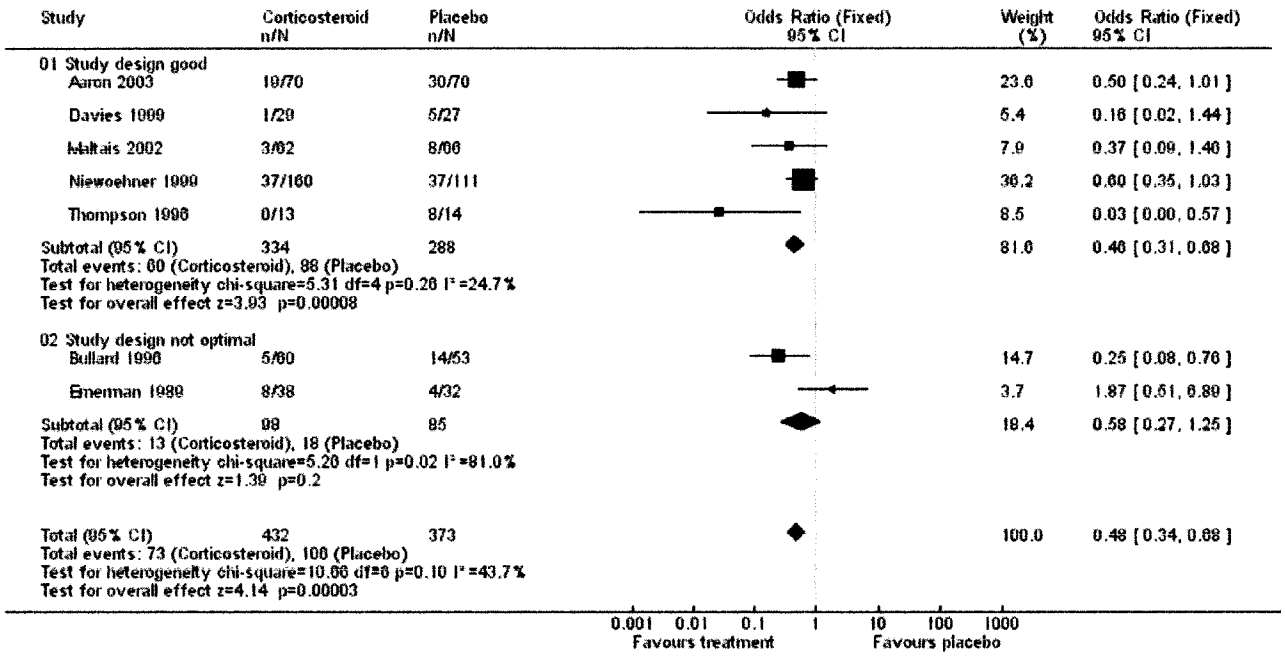

Fig. 1. Meta-analysis of clinical trials that compared the effect of oral corticosteroids versus placebo in preventing exacerbations of chronic obstructive pulmonary disease. The pooled results indicate a benefit from oral corticosteroids. CI = confidence interval. DF = degrees of freedom. (From Reference 60, with permission.)

Two observational studies lasted several years and looked at the long-term FEV_1 decline associated with OCS use in stable COPD. Postma et al[58] studied 139 COPD patients for up to 24 years, and they suggested that the FEV_1 decline appeared slower during periods of higher OCS dosing. Renkema et al followed 58 COPD patients for 2 years.[59] Those on either OCS or ICS therapy had fewer symptoms than patients who did not receive corticosteroids, but there was only a nonsignificant trend toward a slower FEV_1 decline.

In contrast to stable COPD, in which only small subgroups appear to be responders to OCS therapy, the data are much stronger in support of more widespread use of OCS therapy during AECOPDs. These data are summarized in Figure 1 as a meta-analysis, which shows a significant reduction in treatment failures and a more rapid FEV_1 improvement when either oral or systemic corticosteroids are given as part of the AECOPD treatment regimen.[60] The study by Niewoehner et al further showed that 2 weeks of OCS therapy during an AECOPD was just as effective as an 8-week regimen.[61]

ICS were introduced over 25 years ago, initially for treating asthma. ICS, however, have increasingly been given to COPD patients, often to those on long-term OCS therapy, as a way of reducing the oral dose. Supporting this approach are 3 studies that compared short-term OCS and ICS therapy effects on FEV_1. They found that though OCS effects were more prominent, ICS therapy had measurable benefit.[55–57]

A review by van Grunsven et al, in 1999, of 3 placebo-controlled studies with 2-year FEV_1 assessments suggested that ICS therapy improves FEV_1 more than does placebo.[62] A more recent meta-analysis of larger studies by Highland et al, however, showed that FEV_1 decline was not affected by long-term ICS use in COPD (Fig. 2).[63] One 24-week study suggested that adding a long-acting β agonist to ICS therapy would produce a greater FEV_1 response than either agent alone.[64] Supporting this combination approach is the recent observation that withdrawing the ICS component from a combined long-acting-β-agonist-plus-ICS product worsened symptoms.[65]

In contrast to FEV_1 effects, these large trials of ICS therapy in COPD patients did show a significant reduction in AECOPDs with long-term ICS use. This was clearly shown in a meta-analysis by Alsaeedi et al, in 2002 (Fig. 3).[66] A meta-analysis by Sin et al, in 2003, came to a similar conclusion and also demonstrated that long-term ICS use in COPD patients improved quality-of-life scores.[3] Interestingly, the reduction in exacerbations appears to be most prominent in patients who have the most severe reductions in FEV_1.[3]

Importantly, none of these meta-analyses have shown a mortality benefit from long-term ICS therapy. However, in 2 database reviews there was a suggestion that COPD patients who use ICS had a lower mortality than those not taking them, though the studies might have suffered from selection bias.[3] Another large database review suggested that combining ICS with a long-acting β agonist might

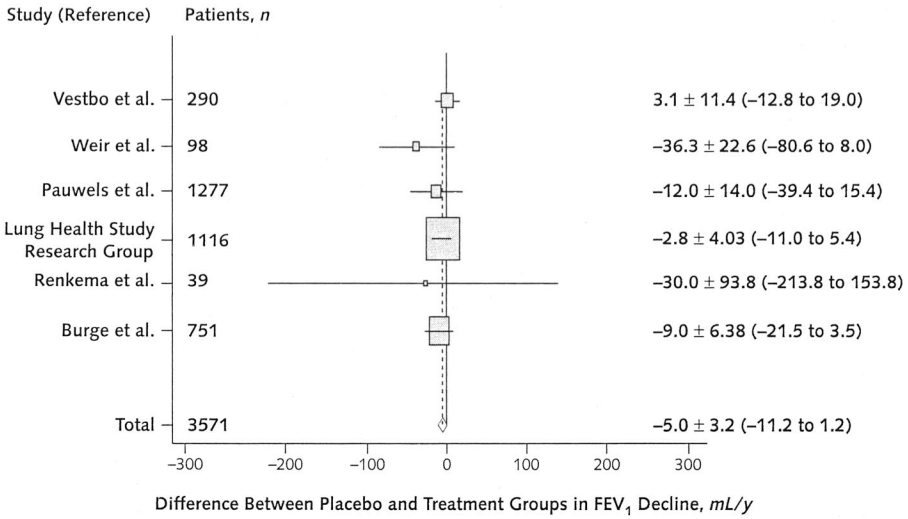

Fig. 2. Meta-analysis of clinical trials that compared the effect of inhaled corticosteroids versus placebo on decline in forced expiratory volume in the first second (FEV_1). The pooled results indicate no benefit from inhaled corticosteroids. (From Reference 63, with permission.)

also have a mortality benefit.[67] This combination of ICS plus long-acting β agonist might also further reduce exacerbations, compared to ICS alone.[64]

Recommendations

Several large professional organizations have formulated recommendations to make some clinical sense of the large amount of data that has accumulated over the last 50 years regarding corticosteroid use in COPD. Two of these, reviewed below, are from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) consortium[8] and the American Thoracic Society and European Respiratory Society (ATS/ERS).[9]

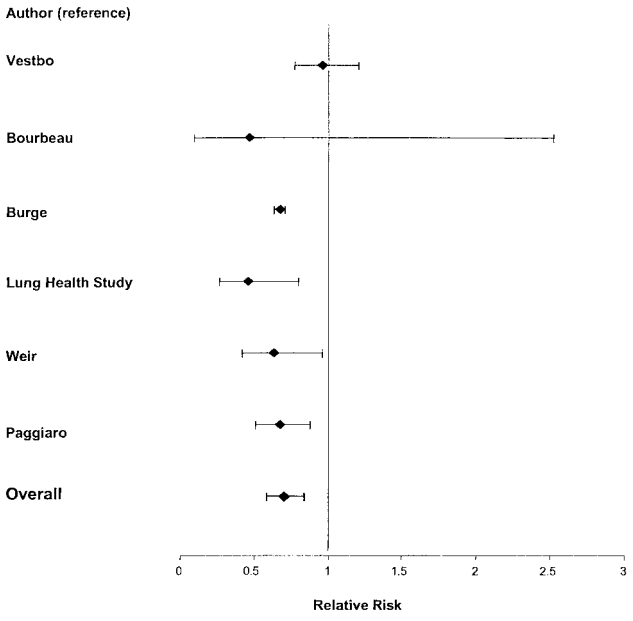

Fig. 3. Meta-analysis of clinical trials that compared the effect of inhaled corticosteroids versus placebo on preventing exacerbations of chronic obstructive pulmonary disease. The pooled results indicate a benefit from inhaled corticosteroids. (From Reference 66, with permission.)

For stable COPD the ATS/ERS guidelines recommend ICS use with patients whose FEV_1 is $< 50\%$ of predicted and who have AECOPDs more than once a year. There is also the suggestion that persistent symptoms despite long-acting bronchodilators might warrant a trial of ICS therapy. With a hospitalized patient, during an AECOPD the ATS/ERS recommend OCS at 30–40 mg/d, and if that is not effective, use intravenous corticosteroids for up to 14 days.[9] The ATS/ERS recommendations also state that you could consider ICS therapy in its place, although minimal data support this substitution.

The GOLD consortium recommends that, for stable COPD, ICS therapy should be used with patients who have an FEV_1 of $< 50\%$ of predicted and who have had more than 3 AECOPD over the last 3 years. The GOLD recommendations also state that ICS therapy might be helpful for symptoms (but not FEV_1) in some patients who are poorly controlled with bronchodilator therapies. During AECOPDs, GOLD recommends using OCS therapy in patients whose baseline FEV_1 is $< 50\%$ of predicted. The recommended dose is 40 mg/d for 10 days. ICS therapy for AECOPDs may be acceptable if the patient is not acidemic.

Interestingly, both ATS/ERS and GOLD recommendations specifically state that there is no place for long-term OCS therapy in stable COPD. However, as noted above, there does appear to be a small fraction of COPD patients who are oral-steroid dependent. Whether these patients

represent a steroid-dependent asthmatic-like subgroup or are simply patients who have not been appropriately and aggressively weaned from OCS therapy after an AECOPD is not clear. Although neither ATS/ERS nor GOLD recommendations specifically address this clinical problem, it would seem reasonable to recommend that every effort should be made to wean the OCS dose, often with the help of ICS therapy, to as low a dose as possible.

Summary

Although pathologically and biochemically different than the inflammation of asthma, the chronic inflammation of COPD, especially in subgroups with asthma-like features, and especially during exacerbations, might be expected to respond to corticosteroid therapy, as does asthma. Complications from long-term corticosteroid use are substantial but appear to be less when given via the inhaled route. Clinical evidence is particularly strong supporting the use of inhaled corticosteroids to prevent exacerbations and oral corticosteroids to reduce the duration and impact of exacerbations. Guidelines from organizations such as the American Thoracic Society and the Global Initiative for Obstructive Lung Disease can be accessed on the Internet to guide therapy.

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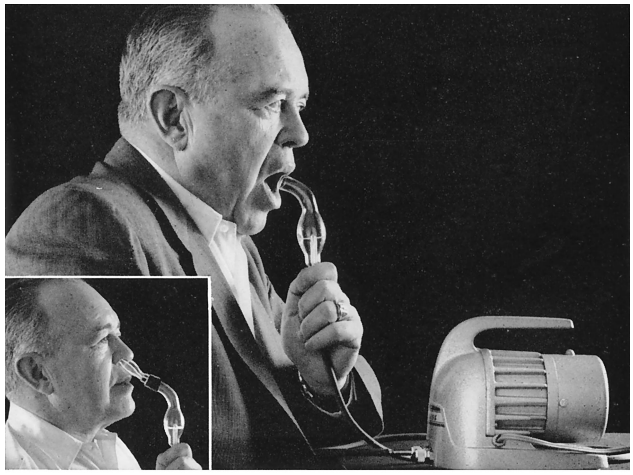

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