Reducing the Frequency and Severity of Exacerbations of Chronic Obstructive Pulmonary Disease

Peter M. A. Calverley

Department of Medicine, University Hospital Aintree, Clinical Sciences Centre, Liverpool, United Kingdom

Exacerbations contribute significantly to impaired health status in chronic obstructive pulmonary disease (COPD), but current therapy can prevent these episodes. Immunization against, for example, influenza offers specific prophylaxis for a minority of episodes. Pulmonary rehabilitation reduces hospital attendance, but its effect wanes. Inhaled bronchodilators such as tiotropium produce similar reductions in exacerbation frequency. Database studies show an association between prescription of inhaled corticosteroids and reduced hospitalization in the older population, a finding confirmed by randomized trials in patients with an FEV1 of less than 50% predicted. Three 1-year randomized clinical trials studied the effect of combining a long-acting β-agonist with an inhaled corticosteroid. In these studies, exacerbation frequency was lower with therapy than placebo. Combination therapy had a similar effect to its monocomponents in the trial of inhaled steroids and long-acting β agonists study using salmeterol and fluticasone. However, when patients with more severe COPD (an FEV1 of less than 36% predicted) were studied using a combination of budesonide and formoterol, a clear improvement was seen in the overall exacerbation rate compared with the β-agonist alone. In addition, the time to first exacerbation was increased compared with either drug alone. Health status changes mirrored these effects. In summary, combination therapy can effectively prevent exacerbations in patients with more advanced COPD.

Keywords: chronic obstructive pulmonary disease; exacerbation; therapy; combination therapy; corticosteroid; bronchodilator

Exacerbations of chronic obstructive pulmonary disease (COPD) are a common cause of ill health, hospitalization, and death. Patients who exacerbate frequently have worse health-related quality of life than those who do not (1), a finding that may contribute to the relationship between impaired health-related quality of life and mortality in COPD (2). This article reviews some of the current strategies used to prevent exacerbations and considers recent data that support the role of regular therapy as an effective prevention strategy.

Before considering this, it is worth emphasizing that most data have been collected using the operational definition of an exacerbation of COPD, which was published recently (3). The comparability of defining exacerbation in this way with previous attempts at definition has not been studied in depth. Data collected in the original studies of antibiotics in exacerbations of COPD adopted a different symptom-based approach (4), a strategy that has been followed in the observational cohort of COPD exacerbations reported from London, United Kingdom (5). Further work to clarify the issues of comparability when episodes are assessed in this way is urgently needed as is a tool, possibly based on regular diary card recording, which can capture all of the episodes of COPD exacerbation. Present data suggest that a significant number of exacerbations are unreported. As such, the numbers of episodes in the placebo studies quoted in this review are likely to be a minimum estimate of the impact of the disease rather than an overestimate. Finally, exacerbations identified by the consensus definition increase in number as disease severity, defined spirometrically, worsens (6). Thus, most interventions have been studied in patients with more severe disease where the events of interest are more likely to occur.

NONPHARMACOLOGIC STRATEGIES IN THE PREVENTION OF COPD EXACERBATION

Although smoking cessation has clear benefits for all patients with COPD, the evidence that it reduces the number of exacerbations is scant. This reflects the fact that most studies are reported in smoking cessation programs in patients at an earlier stage in the natural history of their condition when exacerbations, defined operationally as an increase in symptoms that requires medical intervention, are less frequent. It is highly likely that smoking cessation does reduce the number of exacerbations even in severe disease because an acknowledged effect is a reduction in cough and sputum production. These variables are important predictors of the risk of frequent exacerbations at least in the London observational cohort (7). It should now be possible to test whether clinically important exacerbations are less frequent in those who stop smoking given the advent of more effective strategies to encourage smoking cessation. There is widespread acceptance that vaccination against influenza during the influenza season is a highly cost-effective way of reducing the number of exacerbations both in COPD and asthma. This is recommended in all existing treatment guidelines and should be a routine consideration in people with a diagnosis of COPD at any stage of their disease progression.

Oxygen treatment has been reported to be associated with fewer exacerbations of COPD at least in a large Scandinavian Registry study (8). Pulmonary rehabilitation is also an effective way of reducing hospitalizations because of exacerbation when applied to a cohort of patients with more severe COPD (9). This observation is important, as it suggests that treatment directed at improving well being and reducing breathlessness can be associated with a change in healthcare behavior, that is, the need for hospitalization. It appears unlikely at present that there are specific intrapulmonary effects of undergoing rehabilitation. Rather, it is more likely that such a reduction in exacerbations follows from an increased ability to cope with the symptoms that accompany them. This is an important consideration when reviewing the potential action of pharmacologic therapy where different classes of drug with differing mechanisms of action have been shown to prevent exacerbations from occurring.

More recently, the effects of standardizing treatment and improving patient’s knowledge as part of a disease management program have been studied (10). A 40% reduction in hospitalization was seen in patients who participated in the supported self-management program. A similar reduction in the number of emergency room attendances and unscheduled physician visits was seen in the active treatment limb. Whether these dramatic
changes in behavior can be sustained beyond the constraints of a clinical trial or replicated outside of Quebec remains to be established.

INHALED BRONCHODILATOR THERAPY

For many years short-acting inhaled bronchodilators have been used to control symptoms in COPD, but it has been difficult to establish whether they had an effect on the number of exacerbations that patients experience. One large retrospective study found that including a short-acting anticholinergic in the treatment algorithm was associated with fewer exacerbations (11). This was also a cost-effective option, although data collected retrospectively must always be viewed cautiously when cost-effectiveness is evaluated.

The increasing acceptance that the use of long-acting inhaled bronchodilators is a more effective way of maintaining symptom control in COPD has also led to studies of their effects on exacerbation frequency. Evidence from several studies has indicated that long-acting inhaled β₂-agonists (LABAs) such as salmeterol and formoterol can increase the time before the next exacerbation or exacerbation surrogate, for example, “bad days” in the formoterol studies (12–14). These drugs are given twice daily and have a sustained bronchodilator effect throughout the 12 hours between treatments. Tiotropium is a long-acting inhaled anticholinergic whose clinical effect lasts for at least 24 hours, and this drug has also been shown to reduce the number of exacerbations in those who received active treatment rather than placebo (15). Further studies comparing this drug with four times daily ipratropium have also shown that there were fewer exacerbations in the people taking the long-acting drug (16). Unfortunately, exacerbations in these studies were defined from the patients’ reports of adverse events in the investigator manual. This is likely the explanation for the rather lower numbers of events quoted than in studies where exacerbations were specifically inquired about at each patient visit. Nonetheless, the reduction in hospitalizations, which seem to be a consistent finding with this drug, does suggest that tiotropium has a clinically relevant action.

Comparator data using different pharmacologic classes of drug are now becoming available. In a recent study, which included some previously published data (17), tiotropium treatment was accompanied by significantly fewer exacerbations than was the case with regular short-acting bronchodilator therapy. This was not true for the salmeterol limb of the study, although the number of exacerbations was not significantly different between active treatments (18). The number of events reported here was greater in all groups than seen in the earlier studies involving tiotropium, despite a similar definition, and thus, it may be prudent to await further data before concluding that one agent is preferable.

There are legitimate concerns that both classes of drug may be associated with an increased incidence of cardiovascular events (19, 20), although it is difficult to overcome a confounding by severity bias in studies of this type. On balance, the benefits of preventing exacerbations as part of the overall management plan outweigh the theoretical risk in these more disabled patients.

ICS

Although ICSs do not modify disease progression in COPD (21), there is increasing evidence that they reduce the number of exacerbations experienced by patients with more severe disease. One study in patients with milder disease using an especially sensitive definition of an exacerbation suggests that withdrawal of treatment may precipitate these events (22). However, most data come from studies using the operational definition already referred to and demonstrate that ICSs are effective only in patients with more severe disease (an FEV₁ of less than 50% predicted). This was most clearly shown by further analysis of the original Inhaled Steroids in Obstructive Lung Disease data (6) and has been confirmed in a series of comparative studies, not just with placebo, but also with other active therapies (discussed later here). Data describing the relative benefits of ICS in unslected patients have emerged from retrospective reviews of large databases in Canada and the United Kingdom. The Canadian data were based on patients who were over 65 years of age, and a comparison was made between those patients who were prescribed ICS after admission for an exacerbation of COPD and those who were not. There was a clear advantage in terms of risk of subsequent hospitalization among those to whom ICS had been administered (23). Equally striking is the finding of a reduced mortality in patients where ICSs have been prescribed compared with patients who did not receive ICSs (24). In the latter study, based on the General Practice Research database in the United Kingdom, individuals who received in addition a LABA had a further statistically significant reduction in the risk of dying. Although these studies cannot be considered to be controlled trials, they serve to generate the hypothesis that combining treatments may be more beneficial than using either alone (25).

COMBINATION THERAPY TO PREVENT EXACERBATIONS

To date, three large studies have examined the effects of a combination of LABA and ICS on the risk of developing exacerbation in COPD. These trials had similar formats in that the patients were randomized to combination treatment, to monocomponents, or to an identical placebo. At present, two have been published in full, and one is available in abstract form (26–28).

All were large studies in patients who were current or ex-smokers of cigarettes. Recruits were required to have a history of exacerbations of COPD in the previous year and who could continue with other therapy provided that it was not one of the trial drugs. From the basic demographics of the patients in these trials (Table 1), it is clear that patients who were in studies involving budesonide/formoterol combination had comparatively poorer lung function (a mean FEV₁ of approximately 36% predicted). The other characteristics were generally similar, although fewer participants in the study by Szfranski and colleagues (27) had received treatment with either of the monocomponents than was the case in the other two trials.

The format adopted in these studies was generally similar. The trial of inhaled steroids and long-acting β₂-agonists (26) and Szfranski (27) investigations first asked patients to attend for a 2-week run-in period during which their previous therapy was withdrawn and their clinical stability was confirmed. Thereafter, patients were randomized to one of the four limbs of the study and were followed with measurement of lung function, health status, and a clinical review to determine whether an exacerbation had occurred. In the study by Calverley and colleagues (28), a different approach was adopted in which patients were first administered an oral corticosteroid, 30 mg daily for 2 weeks plus 18 µg of formoterol to try and “optimize” therapy before randomization occurred. In this study design, the anticipated outcome was that lung function and health status would deteriorate to baseline levels in those receiving placebo, and it was anticipated that patients with monocomponents would lie inter-
mediate to the combination treatment, which was anticipated to be the most effective.

The numbers of exacerbations occurring in patients randomized to placebo treatment in these three trials are shown on Table 2 together with the effectiveness of therapy in terms of reduction of exacerbation number relative to placebo. Also reported are those exacerbations that were treated by courses of oral corticosteroids. These events are generally regarded to be clinically more severe than those where antibiotics alone have been employed. In the TRISTAN study, it is clear that each of the active treatments reduced exacerbation frequency to a similar degree, although numerically this effect was greatest in the combined-therapy group. Patients in this study had less severe lung function impairment (Table 1), and also fewer exacerbations occurred during placebo treatment than had been anticipated. Further analysis of these data is ongoing, and it appears that among patients with more impaired lung function, there is a difference between the LABA and the combination treatment in favor of the latter. The patients receiving combination therapy were less likely to report an exacerbation than those receiving the LABA alone. Further presentation of these data is awaited so that the magnitude of these changes can be evaluated with accuracy.

The patients treated with the budesonide/formoterol combination in the reservoir inhaler reported more exacerbations during placebo treatment than in the TRISTAN study, as would be expected from the relative degree of lung function impairment. The number of events was similar in both trials using this treatment despite the difference in design, with relatively little impact of the inhaled formoterol alone but a more striking effect on exacerbation numbers in those patients treated with the combination. Although budesonide alone had a larger effect than formoterol, it was not as effective as the combination therapy in reducing exacerbations. One advantage of the treatment optimization study design is that it allows a more accurate assessment of the time to first exacerbation and this was a prespecified endpoint in the study reported by Calverley and colleagues (28). Exacerbations in this trial were delayed in onset significantly during treatment with the combination therapy, and this was true for all exacerbations, including those requiring treatment with oral corticosteroids. Budesonide alone did not have any effect on the time taken for the next exacerbation of any type to occur. The drug, however, did appear to delay the time of onset of the first exacerbation requiring oral corticosteroid treatment, but it was still inferior to combined therapy in this respect.

Supportive evidence for these effects with all the combination treatments is seen from review of the diary card data on symptoms and also from examining the lung function data. In these studies, there is a clear order effect in terms of lung function change with the combination being superior to LABA then to ICS and, finally, placebo. Data from the health status measurements also follows the same trend, being most striking in the study where treatment was optimized before randomization.

LESSONS FOR THE FUTURE

There is now a large body of data on exacerbations of COPD and the different strategies used to prevent them. In general, such strategies with a LABA or ICS appear to be at least additive in their effectiveness and would normally be combined in the individual patient regardless. Preventing exacerbations appears to be a helpful and unanticipated by-product of persuading the patient to stop smoking and participating in a pulmonary rehabilitation program. Influenza vaccination is clearly cost effective but only prevents exacerbations that are related to infection with this virus. Treatment to control symptoms with long-acting bronchodilators also appears to be helpful. The newer studies where an ICS has been added onto the effects of long-acting bronchodilator treatment are encouraging. Using our current operational definition of an exacerbation in which the clinical consequences of the episode are used to define its occurrence, it is clear that patients whose FEV1 is below 50% predicted benefit from the addition of an ICS on top of the routine maintenance treatment with a LABA.

The dose of corticosteroid used does not need to be very large. Most studies using inhaled fluticasone have reported data

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Exacerbations per Year in the Placebo Group (OCS Treated)</th>
<th>% Reduction LABA</th>
<th>% Reduction ICS Only</th>
<th>% Reduction Exacerbation Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All</td>
<td>OCS Only</td>
<td>All</td>
</tr>
<tr>
<td>TRISTAN (26)</td>
<td>1.30 (0.76)</td>
<td>20</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Szafranski and colleagues (27)</td>
<td>1.80 (1.07)</td>
<td>4</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Calverley and colleagues (28)</td>
<td>1.80 (1.14)</td>
<td>+3</td>
<td>12</td>
<td>24</td>
</tr>
</tbody>
</table>

Definition of abbreviation: Combination = budesonide/formoterol in the same inhaler device; ICS = inhaled corticosteroid maintenance treatment; LABA = long-acting inhaled β-agonists; OCS = oral corticosteroid-treated exacerbations; TRISTAN = trial of inhaled steroids and long-acting β agonists.

---

**TABLE 1. DEMOGRAPHICS OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN CLINICAL TRIALS WITH COMBINATION THERAPY WITH LONG-ACTING β₂-AGONISTS AND INHALED CORTICOSTEROIDS**

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Smoking Currently (%)</th>
<th>FEV₁ (% Predicted)</th>
<th>Reversibility (% Predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRISTAN (26)</td>
<td>1,445</td>
<td>73</td>
<td>75</td>
<td>51</td>
<td>44.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Szafranski and colleagues (27)</td>
<td>812</td>
<td>64</td>
<td>79</td>
<td>35</td>
<td>36</td>
<td>5.3</td>
</tr>
<tr>
<td>Calverley and colleagues (28)</td>
<td>1,022</td>
<td>64</td>
<td>76</td>
<td>35</td>
<td>36</td>
<td>6</td>
</tr>
</tbody>
</table>

**Definition of abbreviation: TRISTAN = Trial of inhaled steroids and long-acting β agonists.**
with 500 µg given twice daily. A 400-µg dose of inhaled budesonide appears to be as effective, at least when combined with the LABA formoterol. In all of these trials, the safety profile has been very encouraging, although residual uncertainty about the long-term consequences of an ICS still leads to a conservative approach to this treatment among many clinicians. The magnitude of any potential adverse effect is very difficult to judge in this patient population where osteoporosis and osteopenia are extremely common even among patients who have not received corticosteroid therapy.

Whether the beneficial effects of adding in an ICS represent a molecular action such as the upregulation of β-adrenoceptors or are simply the consequence of the independent “bronchodilator” effects of each agent is not resolved. These trials do indicate, however, that combining treatments can diminish exacerbation frequency and is certainly something to be considered in patients who have reported exacerbations on a regular basis but have not yet received ICS or LABA therapy in combination.

References