Modulation of airway inflammation to prevent exacerbations of COPD

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ABSTRACT: Exacerbations of chronic obstructive pulmonary disease (COPD) are periods in the chronic course of this disease with symptoms of intensified inflammation, induced in part by infections but also by noninfectious irritating mechanisms. Although these exacerbations seem to be linked to accelerated long-term disease progression and impaired quality of life, there are only limited preventive measures available, apart from smoking cessation.

This article compares the effectiveness of different pharmacological treatments for the prevention of COPD exacerbations, including the oral bacterial lysate OM-85.

Given the differences in the mechanism of action of the treatments discussed, this opens some hope for additive or potentiating effects with combined treatments, which will have to be studied in future controlled trials.

KEYWORDS: Chronic obstructive pulmonary disease, exacerbation, OM-85, pharmacotherapy, prevention
**PHARMACOLOGICAL PREVENTIVE STRATEGIES**

In recent years, several large-scale clinical trials in COPD have analysed the exacerbation-preventing aspects of different treatments. These include inhaled bronchodilators, inhaled corticosteroids and a limited number of antimicrobial strategies. Most antimicrobial strategies have been used therapeutically in the form of antibiotic treatment during an established exacerbation, apart from vaccinations against influenza and pneumococci, which can protect from these infections which are particularly dangerous for COPD-patients.

**LONG-ACTING BRONchodilATORS**

The use of short-acting β-agonists *p.r.n.* is generally accepted as standard treatment in COPD [1] and has become the usual pharmacological treatment in the placebo-control arm of randomised controlled trials. Compared to this regimen, several long-acting bronchodilators have been tested in long-term trials of >28 weeks also under the aspect of prevention of exacerbations. These agents include long-acting β-agonists (LABA; formoterol [8, 9] and salmeterol [10, 11]) as well as long-acting anticholinergics (tiotropium) [11–13]. The results of the LABA trials are summarised in table 1. Salmeterol in these studies is the only long-acting β-agonist with a significant effect on the rate of exacerbations, while formoterol, in two daily doses, failed to show such an effect in two trials with a slightly smaller sample size. The trials with tiotropium are listed in table 2. These studies of shorter duration show similar effect sizes for tiotropium in the prevention of exacerbations. Although the effect-size between the tiotropium and the salmeterol trials cannot be compared directly, the patient populations seem to have COPD of similar severity and the effect size seems to be in the same order of magnitude.

Theophylline, although used widely in the treatment of COPD, is not well documented in its efficacy in reducing COPD exacerbations. Many patients in the trials mentioned above were under constant dose regimens with theophylline preparations, but the contribution of this treatment to the overall treatment effect cannot be derived from existing data.

The mechanisms of action of the effective long-term bronchodilators are different. Therefore, it seems as if long-term bronchodilation in itself might protect from AECOPD.

**INHALED GLUCOCORTICOSTEROIDS**

Inhaled corticosteroids (ICS) are potent anti-inflammatory agents and are very effective in this respect against the characteristic inflammation of bronchial asthma. The disease-stabilising and exacerbation-preventing effect in asthma is well documented. However, in COPD with a distinctly different pattern of the chronic ongoing airway inflammation, inhaled steroids have been ineffective in influencing the long-term decline in lung function, which is thought to be a consequence of the chronic inflammatory process, in four large-scale controlled trials [14–17]. On the other hand, several trials have shown systemic prednisone to be an effective treatment for the initial phase of an acute COPD-exacerbation [18, 19]. There seem to be aspects of at least this acute inflammatory response that are responsive to corticosteroids. This led to the analysis of the long-term trials with inhaled corticosteroids in COPD with respect to exacerbation rates. The first of these trials to suggest

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**TABLE 1**

Long-acting β-agonists and chronic obstructive pulmonary disease exacerbations

| Author          | Year | Treatment       | Patients | FEV1 % pred | Exac. Patient yr⁻¹ | δ%    | p-value |
|-----------------|------|-----------------|----------|-------------|---------------------|-------|---------|
| **CALVERLEY [8]** | 2003 | Formoterol 9 µg b.i.d. | 255      | 36          | 0.91                | -20   | NS      |
|                 |      | Placebo         | 256      | 36          | 1.14*               |       |         |
| **SZAFRANSKI [9]** | 2003 | Formoterol 4.5 µg b.i.d. | 201      | 36          | 1.84                |       | NS      |
|                 |      | Placebo         | 205      | 36          | 1.87                |       |         |
| **CALVERLEY [10]** | 2003 | Salmeterol 50 µg b.i.d. | 372      | 44          | 0.54                | -29   | 0.0003  |
|                 |      | Placebo         | 361      | 44          | 0.76                |       |         |
| **BRUSASCO [11]** | 2003 | Salmeterol 50 µg b.i.d. | 405      | 38          | 1.23                | -17   | NS      |
|                 |      | Placebo         | 400      | 39          | 1.49                |       |         |

FEV1: forced expiratory volume in one second; % pred: % predicted; Exac: exacerbations; NS: nonsignificant. *: exacerbations requiring oral steroid treatment.

**TABLE 2**

Tiotropium and exacerbations of chronic obstructive pulmonary disease

| Author          | Year | Treatment       | Patients | FEV1 % pred | Exac. Patient yr⁻¹ | δ%    | p-value |
|-----------------|------|-----------------|----------|-------------|---------------------|-------|---------|
| **VINCKEN [12]** | 2002 | Tiotropium 18 µg day⁻¹ | 356      | 42          | 0.73                | -24   | 0.006   |
|                 |      | Ipratropium     | 179      | 39          | 0.96                |       |         |
| **CASABURRO [13]** | 2002 | Tiotropium 18 µg day⁻¹ | 550      | 39          | 0.76                | -20   | 0.045   |
|                 |      | Placebo         | 371      | 38          | 0.95                |       |         |
| **BRUSASCO [11]** | 2003 | Tiotropium 18 µg day⁻¹ | 402      | 39          | 1.07                | -28   | 0.025   |
|                 |      | Placebo         | 400      | 39          | 1.49                |       |         |

FEV1: forced expiratory volume in one second; % pred: % predicted; Exac: exacerbations.
a protective effect of ICS was the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) trial, with fluticasone 2 × 500 mcg inhaled as metered dose inhaler with a spacer device for 3 yrs [14]. Some further trials with different designs have also directed towards an effect of ICS in protecting against exacerbations of COPD (table 3) [8–10]. This effect seems to be present mainly in those patients with more advanced disease state, as defined by the decline in FEV1.

**COMBINATION TREATMENTS**

The most recent attempts in this regard have included trials with the combined preparations of LABA and ICS [8–10]. Here again, there is some indication of a protective effect of this treatment preventing exacerbations (table 4). The effect size in these treatments was slightly, although not significantly better than that for steroids alone. So far there is a paucity of data documenting the effectiveness of the combination of long-acting anticholinergics (tiotropium) and inhaled steroids, although in many European countries this combination is used in clinical practice in order to obtain an optimal symptomatic control in advanced COPD. There is also a lack of data on the effectiveness of combined LABA and tiotropium in COPD.

**ORAL IMMUNOSTIMULANTS**

Based on a completely different mechanism of action, there have also been trials with OM-85, an oral bacterial lysate treatment, in patients with recurrent exacerbations of chronic bronchitis or mild COPD [20–22]. The mechanism of action of OM-85 has been discussed in detail elsewhere [23–25]. The stimulation of the gastrointestinal lymphatic system, the upregulation of secretory antibodies and the activation of alveolar macrophages influences the immune and inflammatory responses of the respiratory system. This immunostimulant treatment has been prescribed widely for the prevention of respiratory infections during the winter season in several European countries. There have been only a limited number of randomised controlled trials in adults with chronic bronchitis or COPD so far, which will be discussed in more detail (table 5).

The placebo-controlled study by Collet et al. [20] in 381 outpatients with COPD (mean % predicted FEV1 42.3% for OM-85 and 44% for placebo) studied the exacerbation-preventing effect of OM-85 over 6 months. The risk of having an acute infection or the rate of exacerbations was similar in the two groups. However, the severity of the respiratory exacerbations was influenced by this treatment, with the number of days in hospital for lower respiratory tract infections being 55% less in the group treated with OM-85, and the risk of needing hospitalisation was reduced by 30%. The reduction in the severity of these infections is an intriguing effect of this oral treatment, which at least from a health-economic point of view is interesting in the context of COPD [26, 27].

A similar protective effect of the oral immunostimulant was seen in the trial by Orcel et al. [21], who investigated 354

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**TABLE 3**

| Author      | Year | Treatment                  | Patients | FEV1 % pred | Exac. Patient yr⁻¹ | Δ%  | p-value |
|-------------|------|---------------------------|----------|-------------|---------------------|-----|---------|
| Burge [14]  | 2000 | Fluticasone 500 µg b.i.d. | 373      | 50          | 0.99                | -25 | 0.026   |
|             |      | Placebo                   | 370      | 50          | 1.32                |     |         |
| Szafrański [9] | 2003 | Budesonide 200 µg b.i.d.  | 198      | 37          | 1.59                | -15 | NS      |
|             |      | Placebo                   | 205      | 36          | 1.87                |     |         |
| Calverley [8] | 2003 | Budesonide 200 µg b.i.d.  | 257      | 36          | 0.87                | -24 | 0.044   |
|             |      | Placebo                   | 256      | 36          | 1.14                |     |         |
| Calverley [10] | 2003 | Fluticasone 500 µg b.i.d. | 374      | 45          | 0.56                | -26 | 0.0001  |
|             |      | Placebo                   | 361      | 44          | 0.76                |     |         |

FEV1: forced expiratory volume in one second; % pred: % predicted; Exac: exacerbations; NS: nonsignificant. #: metered dose; delivered dose=160 µg.

**TABLE 4**

| Author      | Year | Treatment                  | Patients | FEV1 % pred | Exac. Patient yr⁻¹ | Δ%  | p-value |
|-------------|------|---------------------------|----------|-------------|---------------------|-----|---------|
| Calverley [8] | 2003 | BUD/FOR 320/9 µg b.i.d.   | 254      | 36          | 0.63                | -24 | 0.001   |
|             |      | Placebo                   | 256      | 36          | 1.14                |     |         |
| Szafrański [9] | 2003 | BUD/FOR 160/4.5 µg b.i.d. | 208      | 36          | 1.42                | -24 | 0.035   |
|             |      | Placebo                   | 205      | 36          | 1.87                |     |         |
| Calverley [10] | 2003 | FLUT/SALM 500/50 µg b.i.d.| 372      | 45          | 0.46                | -39 | 0.0001  |
|             |      | Placebo                   | 361      | 44          | 0.76                |     |         |

FEV1: forced expiratory volume in one second; % pred: % predicted; Exac: exacerbations; BUD: budesonide; FOR: formoterol; FLUT: fluticasone; SALM: salmeterol. #: exacerbations requiring delivered doses; #: exacerbations requiring oral steroid treatment.
elderly subjects with chronic bronchitis, living in institutions for the elderly. Only a subgroup had significant COPD, but all had a history of at least four bronchitis exacerbations in the year before entering the study. They found a 28% reduction in the number of lower respiratory tract infections and antibiotic prescriptions in the OM-85 treated group. This effect was entirely due to a reduction in the rate of bronchitis exacerbations, while the number of pneumonias was not different between the groups.

The most recent randomised controlled trial, presented only in abstract form [22], studied the protective effect of OM-85 in outpatients with chronic bronchitis or mild COPD (Global Initiative for Chronic Obstructive lung Disease (GOLD) stages I or II) over 6 months. These patients were selected during an acute bronchitic exacerbation in the autumn and were treated with OM for 30 days, followed by 10 days per month for months 3, 4 and 5. Again, there was a protective effect against further acute exacerbations of chronic bronchitis with a 29% reduction in the number of exacerbation-events per patient in the active treatment group by the end of the treatment period.

In the setting of chronic bronchitis and mild-to-moderate COPD, therefore, OM-85, given orally for 30 days, followed by 10 days per month in months 3, 4 and 5, seems to protect against bronchitic exacerbations over a period of 6 months. These studies were all conducted over the winter season, while no longer treatment periods with this bacterial lysate have been studied so far. The effect size of this treatment was comparable to that of inhaled steroids or LABA, although the study populations were not directly comparable. The studies available so far with this oral bacterial lysate have been assessed in a recent meta-analysis [28]. When only the three most recent and best quality studies were combined, the number needed to treat to prevent an exacerbation was calculated to be ~15.4 (95% CI 5.5–∞) [28]. Overall, there is still a paucity of studies in patients with a well-defined COPD in advanced GOLD-stages and a lack of studies longer than 6 months.

OUTLOOK
As the mechanism of action of OM-85 is distinctly different from that of the inhaled “standard-treatments” for chronic obstructive pulmonary disease, the question comes up, if the combined use of an effective inhaled anti-inflammatory regimen and/or bronchodilator regimen and the immunomodulating oral OM-85 might lead to an additive or even better protection from chronic obstructive pulmonary disease-exacerbations. To answer this question, more controlled clinical trials with OM-85 in well defined patients with advanced chronic obstructive pulmonary disease are needed, where preventing an exacerbation can be expected to result in the most prominent cost savings and improvements in quality of life.

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Figure 1. *Eur Respir Review* 14: 94 p. 13. This figure has been redrawn from Bowler RP, Barnes PJ, and Crapo JD. The role of oxidative stress in chronic obstructive pulmonary disease. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2004; 1: 255–277 with permission. Copyright Taylor & Francis Group, 2005.

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