Prevention of COPD exacerbations: medications and other controversies

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\textbf{ABSTRACT} Exacerbations have significant impact on the morbidity and mortality of patients with chronic obstructive pulmonary disease. Most guidelines emphasise prevention of exacerbations by treatment with long-acting bronchodilators and/or anti-inflammatory drugs. Whereas most of this treatment is evidence-based, it is clear that patients differ regarding the nature of exacerbations and are likely to benefit differently from different types of treatment. In this short review, we wish to highlight this, suggest a first step in differentiating pharmacological exacerbation prevention and call for more studies in this area. Finally, we wish to highlight that there are perhaps easier ways of achieving similar success in exacerbation prevention using nonpharmacological tools.

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More targeted pharmaceutical, and perhaps nonpharmaceutical, interventions are needed to prevent COPD exacerbation http://ow.ly/LQFcB

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Introduction
Exacerbations of chronic obstructive lung disease (COPD) are the source of significant suffering for patients, a strain on many healthcare systems and associated with significant costs [1, 2]. Viral infections seem to be implicated in approximately half of all exacerbations and only a quarter of exacerbations seem unrelated to infection [3]. Prevention of COPD exacerbations is an important part of the management of COPD and the most recent strategy document from the Global Initiative for Chronic Obstructive Lung Disease emphasises assessment of risk of exacerbations as a central part of the assessment of any COPD patient [4, 5]. In patients at high risk of exacerbations, management should be aimed at risk reduction. As future exacerbations are best predicted by history of previous exacerbations [6], these patients are often labelled as “frequent exacerbators” [7], and pharmacological treatment is particularly aimed at this patient group [5].

Little has been done in order to identify if certain patients would benefit more from one type of preventive strategy than another. Although perhaps not real personalised medicine, any attempt at a strategy to focus treatment to those most likely to benefit from it will enter into the uneasy area between evidence-based medicine and personalised medicine [8]; i.e. large-scale trials with hard outcomes for personalised treatments are not likely to be performed in the near future, if ever. We wish, nevertheless, to open a discussion on whether such a strategy is feasible based on current knowledge – without claiming that the time is ripe for evidence-based guidance. We also want to highlight that nonpharmacological strategies for preventing exacerbations could potentially have a significant effect on risk reduction.

Preventive pharmacological treatments

Bronchodilators
Long-acting bronchodilators have been shown to reduce exacerbations by 10–20% [5, 9]. Most of the evidence comes from studies including patients with severe to very severe COPD with a history of at least one exacerbation in the year prior to study inclusion. Exacerbation outcomes in these studies have often been broadly defined without limitation in treatment; i.e. exacerbations treated with bronchodilators, systemic corticosteroids and/or antibiotics.

The most likely mode of action of bronchodilators is a reduction in dynamic hyperinflation known to be the mechanism behind the increased breathlessness in many patients [9]. There are few good comparisons between long-acting β₂-agonists and long-acting anticholinergics (LAMAs) but in the POET study, once-daily tiotropium was superior to twice-daily salmeterol in reducing time to first exacerbation [10].

Long-acting bronchodilators are unlikely to have major anti-inflammatory effects [11] and although LAMAs could potentially have a beneficial effect in reducing mucus hypersecretion associated with an increased risk of exacerbations, data supporting this mechanism are sparse. Combining two long-acting bronchodilators leads to significantly better lung function but only marginally improved reduction in exacerbation risk [12] and it seems unlikely that all COPD patients at risk of exacerbation will benefit from double treatment. We believe that long-acting bronchodilators do not affect the frequency of exacerbations per se; however, through reducing breathlessness, they can be seen to increase the threshold at which a given patient will consider their worsening sufficiently severe to be labelled an exacerbation. This is illustrated in figure 1a and b.

In our view, long-acting bronchodilators are therefore likely to be efficacious in preventing any type of exacerbation independent of origin.

Anti-inflammatory drugs
The rationale behind using an anti-inflammatory drug to reduce risk of exacerbations will probably differ from that of long-acting bronchodilators. The assumed mechanism of action would come from the drug modifying the acute inflammatory response to bronchial infection or exposure to airway irritants accompanying an exacerbation and giving rise to symptoms associated with an exacerbation. For inhaled corticosteroids (ICS), this could result in reduction of eosinophilic inflammation, most often accompanying virally induced exacerbations [3]. This is schematically shown in figure 1c. As anti-inflammatory drugs will be expected to have a lesser effect on lung function, including dynamic hyperinflation, than bronchodilators, it seems reasonable to assume that they may not affect all exacerbations equally. Instead, they will only exert their effect on certain exacerbations, dependent on the inflammatory profile of the exacerbation. Two classes of anti-inflammatory drugs are currently registered for exacerbation prevention, phosphodiesterase-4 (PDE4) inhibitors and ICS.

PDE4 inhibitors
PDE4 inhibitors reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP [13]. In initial studies of roflumilast, the only registered PDE4 inhibitor, there was a limited effect on exacerbations.
However, when inclusion criteria were narrowed to patients with forced expiratory volume in 1 s (FEV1) less than 50% of predicted, chronic bronchitis and a history of at least one treated exacerbation within the last year, studies found a 15–20% reduction of exacerbations treated with systemic corticosteroids [16]. A recent study also found efficacy in patients already treated with a combination of long-acting bronchodilators and an ICS [17]. To date, no study has been carried out with exacerbations treated with antibiotics alone as an outcome. Adverse effects, in particular gastrointestinal problems, are seen more frequently in patients treated with an oral PDE4 inhibitor than in patients receiving inhaled bronchodilators or ICS [5].

Based on current evidence, roflumilast should only be used for exacerbation prevention in patients with an FEV1 less than 50% of predicted, chronic bronchitis and a history of frequent exacerbations treated with systemic corticosteroids. Caution is warranted in patients with low body mass index, due to the risk of weight loss, and in patients with frequent exacerbations characterised by purulent sputum who are treated with antibiotics, as no data on efficacy exist in this patient population.

**Inhaled corticosteroids**

It seems fair to state that ICS were initially used in COPD based on little else than the fact that they worked well in asthma. Subsequent trials showed that they could reduce exacerbations [18–20] but topics such as study methodology [21, 22], mechanism of action and safety [23] remain issues of debate – often heated debate with few nuances [24].

Large-scale trials have shown a reduction in exacerbations treated with systemic corticosteroids and/or antibiotics in patients treated with ICS [18–20]. Except for the TORCH trial [20], and recent trials with a combination of fluticasone furoate and vilanterol [25], virtually all studies showing an effect on exacerbations have included patients with an FEV1 less than 50% of predicted and a history of at least one treated exacerbation in the previous year. In addition, the effect is clearly most significant for exacerbations treated with corticosteroids [20] and some trials have only used corticosteroid treated exacerbations as outcome [26, 27]. It seems obvious that the effect on exacerbations associated with bacterial infection is, at most, negligible. ICS have also been persistently been associated with an increased risk of pneumonia [20, 23, 28, 29], although data indicate that in COPD patients with pneumonia, treatment with ICS is associated with a favourable pneumonia outcome [30]. Many patients currently treated with ICS can be taken off treatment [31]. A recent post hoc analysis of two trials including the ICS fluticasone furoate has
shown that blood eosinophils are markers of increased efficacy of treatment with ICS [32], findings that are supported by studies of biomarkers and response to oral corticosteroids during an exacerbation of COPD [33]. No prospective study has yet used blood eosinophils for treatment guidance and the above findings, so far, only relate to patients seen in secondary and tertiary care.

Based on current evidence, ICS should only be used for exacerbation prevention in patients with an FEV1 less than 50% of predicted and a history of frequent exacerbations treated with systemic corticosteroids. We have deliberately stated both criteria, as we believe that low lung function, in itself, is too weak a predictor of future exacerbations, and evidence in subjects with an FEV1 >50% is still too weak. ICS could be considered in patients with more preserved lung function if they have a history of frequent exacerbations with clear efficacy of systemic corticosteroids. Caution is warranted in patients with frequent exacerbations characterised by purulent sputum and treated with antibiotics. In these patients, as well as in patients with a history of recent pneumonia, treatment should be restricted to subjects with an eosinophil count of 300 or more per µL in peripheral blood in the stable phase.

**Antibiotics**

Antibiotics may reduce risk of exacerbations in patients with lower airway colonisation, and frequent exacerbations characterised by increased phlegm, purulent sputum and fever/malaise. Efficacy has been shown for fluoroquinolones and macrolides; for the latter, not just on exacerbations related to lower respiratory tract bacterial infection [34, 35].

However, whereas most drugs may lead to adverse events in the patient taking the drug, the prophylactic use of antibiotics is associated with a risk of harm to others through an increase in antibiotic resistance related to more widespread use of antibiotics [36]. Subgroup analyses of the largest efficacy trials of azithromycin showed that this drug was least efficacious in patients already on recommended preventive therapies, patients with more severe disease and active smokers [35, 37].

Based on current evidence, we would recommend not to use macrolides for exacerbation prevention in these subgroups of patients and to stop treatment in patients where an effect is not obvious within 6 months at the most.

**Comment**

We are well aware that the above suggestion for a more narrow selection of patients to be treated with anti-inflammatory drugs is controversial and, to some, provocative. We fully accept that the evidence base is weak and that far more studies are needed before evidence-based guidance can be issued. However, we doubt that more restrictive large-scale trials are likely to be carried out in large numbers in the near future, and without a push to start implementing knowledge from various other sources, we are unlikely to progress and serve our patients. We need to get away from simplistic discussions and urge clinicians, as well as the pharmaceutical industry, to accept that patients in daily clinical practice vary much more than the study populations included in usual efficacy trials on which we base our recommendations.

**Preventive nonpharmacological treatments**

Pulmonary rehabilitation delivered in a stable state is an established component of COPD management, and aims primarily to reduce symptoms, improve functional capacity and increase patient participation [38]. Studies indicate that it also may reduce the frequency and duration of subsequent exacerbations [39]. Rehabilitation delivered in the post-acute recovery stage may also reduce the risk of readmissions and even mortality [40], although a recent large pragmatic trial questions whether these results can be generalised [41, 42].

Vaccination is another area that could deserve attention. Influenza vaccination has been highlighted as a possible means for reducing exacerbation rates. Still, only one randomised controlled study has specifically studied influenza vaccination in COPD patients [43]. In this study, rate of hospitalisations due to influenza and pneumonia was significantly reduced (adjusted risk ratio 0.48, p=0.008), as was risk of death (adjusted odds ratio 0.30, p<0.001); no effect on outpatient visit frequency was found. A Dutch study has considered influenza vaccination cost-effective in patients with chronic lung diseases [44] and, indeed, most countries now include patients with chronic lung diseases among those who should receive vaccination. Considerable benefits have also been shown for pneumococcal vaccination [45, 46] but, again, the evidence base is limited. Studies of oral vaccination against *Haemophilus influenzae* have shown conflicting results and, in general, the evidence for effectiveness does not suggest the widespread use of these vaccines [47].

However, simpler measures are also likely to have an effect on reducing risk of exacerbations, morbidity and mortality in COPD [48]. As up to 50% of exacerbations are related to viral infections, focus on hand hygiene seems warranted, as this can reduce transfer of infection [49]. Another factor relates to clothing. In his review, Burge [48] shows how proper clothing is associated with better survival in winter months. It
seems probable – but is poorly documented – that caring for sick grandchildren may increase the risk of viral infections and exacerbations in the elderly COPD patient. However, whether risk avoidance is feasible in this situation is a different matter.

Conclusion
Exacerbations are important events in COPD. There is a clear need for more targeted pharmacological exacerbation prevention – even with existing drugs – and there is a clear need for more studies in this area. In addition, there are perhaps easier ways of achieving similar success in exacerbation prevention using nonpharmacological tools.

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