EDITORIAL

The role of the phosphodiesterase-4 inhibitor, roflumilast, in chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. TORCH (Towards a Revolution in COPD Health)[1], INSPIRE (Investigating New Standards for Prophylaxis in Reducing Exacerbations),[2] and UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium)[3] are large, adequately powered, multi-centre trials that have been published in the past 5 years and have shown a number of therapies to be effective in the management of COPD. These include long-acting inhaled β-agonists and anticholinergic therapies such as bronchodilators, inhaled corticosteroids, and the combination of β_2-agonists with inhaled corticosteroids. The outcomes observed with these therapies include a reduction in exacerbations,[1,3] improvements in the quality of life,[1-3] and borderline reductions in mortality.[1,3] However, the magnitude of improvements in such outcomes as exacerbations has been limited to a reduction in exacerbation frequency of approximately 20% to 25%. Effects on COPD progression in the form of a reduction in the forced expiratory volume in 1 second (FEV_1) decline have been more difficult to show with these therapies, and only in a secondary analysis of the TORCH dataset was an effect on reduction of FEV_1 decline seen with combination therapy.[1,4]

Thus, there is an urgent need for new classes of treatments for patients with COPD and especially novel anti-inflammatory agents that may have disease-modifying actions in this condition by reducing airway inflammatory processes. Phosphodiesterase (PDE) inhibitors have recently been the focus of attention in COPD because PDEs are a large group of enzymes that inhibit the ubiquitous intracellular cyclic adenosine monophosphate.[5] As these enzymes play such an important part in metabolism, their inhibitors are attractive targets for drug development. PDE4, for example, is one of the main enzymes involved in metabolism and inflammation within the airways.[6] Thus, there has been a considerable interest in PDE4 inhibitors in airway disease, first with cilomilast and currently with roflumilast. The previous smaller studies with cilomilast showed a beneficial effect on lung function,[7] while the studies with roflumilast showed that exacerbations could also be reduced, though these reductions were not consistent across exacerbation severities.[8,9]

However, a post-hoc analysis of the study by Calverley et al., published in 2007, suggested that roflumilast could reduce exacerbations in a subtype of COPD patients, namely patients with more severe airflow obstruction and more frequent exacerbations.[9] Thus, in 2 further randomized controlled trials combined in a single paper and recently published, Calverley et al. describe the effect of roflumilast on lung function and exacerbations in patients with FEV_1 less than 50% predicted, chronic cough and sputum production, and at least 1 recorded COPD exacerbation treated with oral corticosteroids and/or treated in hospital in the past year.[10] This is an interesting design because COPD patients with a history of bronchitis and frequent exacerbation were for the first time recruited to a major trial, and we have shown that these patients are more likely to have increased airway inflammation compared with patients with infrequent exacerbations.[11] This is also the group of patients with frequent exacerbations where one would expect anti-inflammatory therapies to have most effect and where the therapy can be most cost-effective by preventing hospital admission.

When combined, the results of these studies showed that the prespecified primary endpoints

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of lung function improved with roflumilast compared to placebo and also that there was a 17% reduction in the rate of moderate and severe COPD exacerbations.[11] There was an increase in study withdrawal in patients on roflumilast compared with placebo and, as noted in the earlier studies, more gastrointestinal adverse effects were observed in the roflumilast-treated patients. Of note, patients on roflumilast were more likely to lose weight especially if they were obese, though the reason for this effect is not clear and requires further investigation. In the same issue of the *Lancet*, Fabbri et al. describe another pair of studies in which roflumilast was added either to salmeterol or tiotropium.[12] In this study, the patients had FEV_1 of 40% to70% predicted, but the patients in the tiotropium study were more symptomatic and had bronchitic symptoms. In both cases, the addition of roflumilast to either salmeterol or tiotropium improved lung function. In the studies reported in these 2 papers, patients were not treated with inhaled corticosteroids during the study observation period.[10,12] Despite its anti-inflammatory properties, oral roflumilast had no effect on systemic inflammation as measured with C-reactive protein. This result is similar to results from my own group investigating the effects of macrolide erythromycin in COPD, which also had no effect on systemic inflammatory markers.[13]

It can be concluded that the addition of roflumilast in patients with severe COPD and evidence of bronchitis improves lung function and reduces exacerbation frequency. Again, the reduction in exacerbation frequency is similar to that seen in the studies on bronchodilators and inhaled corticosteroids. As patients with evidence of chronic bronchitis have greater airway inflammation, they are the group that needs targeting with new anti-inflammatory therapies. An important question is whether the addition of roflumilast to combination therapy of inhaled corticosteroids and β-agonist or long-acting anticholinergic further reduces exacerbation frequency and improves outcomes, which would be an important advance in COPD management. There have also been no direct comparisons of inhaled corticosteroids and roflumilast with respect to the degree of anti-inflammatory activity and exacerbation reduction, hence further investigation is needed.

The above studies provided consistent results, which suggests that roflumilast is effective in patients with severe COPD, though further monitoring of side effects and weight loss is required. The future of COPD therapy is to use combination therapy especially in more severe symptomatic disease. PDE4 inhibitors have been shown to play a role in COPD and are likely to be particularly effective in combination with other pharmacological agents used in COPD. This may well be the breakthrough that we have been waiting for in recent years.

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