Triple therapy for COPD

Who needs it?

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A stepwise approach to the treatment of patients with chronic obstructive pulmonary disease is recommended. Triple therapy may have a role in this approach for some patients.

Guidelines for treating chronic obstructive pulmonary disease (COPD) generally suggest that combination therapy with dual bronchodilators plus inhaled corticosteroids (ICS) should be reserved for patients with a forced expiratory volume in one second (FEV_1) of less than 50% predicted and repeated exacerbations.[1,2] Australian PBS guidance stipulates the same conditions. In reality, many patients with COPD are using triple therapy, without necessarily a clear indication. Similarly, in studies from the UK it was found that about 50% of patients with COPD were receiving triple therapy within three years of initial diagnosis.[3] A percentage of these individuals will have coexistent asthma (so-called 'asthma-COPD overlap'), but many will neither have frequent exacerbations nor features of asthma. How should these patients be managed? Who requires triple therapy?

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History and development of COPD treatments

Structured management of patients with COPD has been enhanced by the development of both local (COPD-X plan) and global (Global Initiative for Chronic Obstructive Lung Disease [GOLD]) COPD guidelines.[1,2] Initial emphasis was placed on the use of short-acting beta-agonists (e.g. salbutamol) and anticholinergic bronchodilators (e.g. ipratropium bromide), which were then followed by use of a long-acting antimuscarinic agent (LAMA; e.g. tiotropium) or long-acting beta agonist (LABA; e.g. indacaterol) for management of more troublesome symptoms as evidence of efficacy became available.

The use of ICS in COPD preceded evidence for their efficacy, no doubt as a consequence of their well-known beneficial effects in asthma as well as the known (limited) benefits of oral corticosteroids in treating exacerbations. Trials of ICS in the 1990s and early 2000s were aimed at assessing whether therapies reduced decline in lung function, which they did not. They were, however, shown to decrease the risk for exacerbations compared with placebo.[4]

Early studies used high doses of the ICS fluticasone propionate (500 mcg twice daily) alone or in combination with a LABA for great efficacy.[5,6] Similar benefits in terms of exacerbations were observed in studies of budesonide given in doses of 400 mcg twice daily in combination with the LABA formoterol (eformoterol).[7] However, the dose-relationship of ICS in COPD is unknown, unlike in asthma, and there are known risks associated with the use of high doses of ICS in COPD. These include an increased risk of pneumonia, which first became apparent in the three-year Towards a Revolution in COPD Health (TORCH) trial using 500/50 mcg twice daily fluticasone propionate/salmeterol compared with its monocomponents or placebo.[7] High-dose ICS in combination therapy have been widely used, despite an absence of dose-ranging efficacy studies, and has informed development of regulatory recommendations such as those of the PBS.

A paradigm shift in COPD treatment

A study that challenged our thinking about the need for ICS in COPD was published in 2016. The Fluticasone on the Rate of

Exacerbations in Subjects with Moderate to Very Severe COPD (FLAME) study compared a LABA/LAMA combination (indacaterol/glycopyrronium) with a LABA/ICS combination (salmeterol/fluticasone propionate).[8] The study population consisted of patients with an FEV_1 of 25 to 60% and at least one moderate exacerbation of COPD in the previous year. The group receiving the LAMA/LABA combination had a longer time to first exacerbation (71 days *vs* 51 days; hazard ratio, 0.84; p<0.001), representing a 16% lower risk. The annual rate of moderate or severe exacerbations was also 17% lower in the LABA/LAMA combination group (0.98 *vs* 1.19; rate ratio 0.83; p<0.001). Importantly, the incidence of pneumonia was significantly different: 3.2% in the LABA/LAMA group and 4.8% in the ICS/LABA group (p=0.02). Rather unexpectedly, the rate of COPD exacerbations in the LABA/LAMA group compared with the ICS/LABA group was independent of the baseline blood eosinophil count (<2% or ≥2%; or about 150 cells/mcL).

The landmark FLAME study indicated that combination therapy with a LAMA plus a LABA in patients with frequent exacerbations of COPD and an FEV_1 of less than 60% was equally efficacious in reducing exacerbations as a combination ICS/LABA. Another key study also contributed to the building trend. The Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) trial involved judicious back-titration of ICS in suitable patients on triple therapy and showed that this could be done without provoking a worsening of exacerbations or reducing quality of life after cessation of ICS.[9]

These two landmark studies have changed recent attitudes and led to recommendations to either de-escalate ICS therapy or postpone initiation of ICS therapy in most patients with COPD. Many clinicians wonder if triple therapy (ICS/LABA/LAMA) is indicated and in whom, and there remains substantial uncertainty about the patient group likely to benefit. The emphasis in COPD guidelines has also changed; however, another important study has been completed that may again disrupt current thinking about the best management of COPD.

Another paradigm shift in COPD?

The FLAME study may have excluded patients with COPD who were responsive to corticosteroid therapy and therefore could have underestimated the benefits of corticosteroids. Moreover, different inhaler devices were used to administer each drug, which could have influenced the outcomes. There is a need to have head-to-head comparisons eliminating these variables, but the research still needs to mirror everyday clinical practice as far as possible.

These problems have now been tackled in a recent randomised controlled trial of triple therapy administered in the same inhaler, comparing it with its components delivered as an ICS/LABA or a LABA/LAMA combination.[10] The Informing the Pathway of COPD Treatment (IMPACT) trial demonstrated that triple therapy with ICS/LABA/LAMA (fluticasone furoate/vilanterol/umeclidinium) reduced annual exacerbations of COPD by about 25% more than the LABA/LAMA combination (vilanterol/umeclidinium). It was also more effective than the ICS/LABA combination (fluticasone furoate/vilanterol). As in the FLAME study, the incidence of pneumonia was significantly higher in the ICS therapy groups. So, is triple therapy the way forward?

Several important issues may pertain to the results. The IMPACT study has several strengths:

- the same device was used to administer the combination therapies
- a relevant patient population
- real-life design
- near-flawless execution.

However, compared with the FLAME study, a patient population that was sensitive to ICS may have been studied. Why? Almost 70% of patients enrolled in the trial were taking an inhaled glucocorticoid along with their dual bronchodilator therapy. During the run-in period patients were treated with a LABA/LAMA combination only and excluded if they had an exacerbation of COPD, conceivably leaving a population in the study biased to benefit from ICS. This aspect was raised in the accompanying editorial.[11] Also, in contrast to the FLAME study, the IMPACT study found that the benefits of added ICS were greater in patients whose baseline blood eosinophil count was greater than 150 cells/mcL. As almost 60% of patients were in this category, this again suggests that a patient population sensitive to ICS was enrolled.

How should the results of these new studies impact our treatment of COPD?

Where do the results of these recent landmark studies leave us? The area is complex and several issues require consideration. No single study can provide all the answers, and both the FLAME and IMPACT studies have significant shortcomings. The ideal treatment would offer a reduction in exacerbations with minimal side effects. ICS are associated with known adverse effects, including increased pneumonia risk, skin thinning and oropharyngeal candidiasis, as well as the potential for increased bone fractures, cataracts and diabetes.[12]

Importantly, there is increasing recognition that lower doses of ICS than have been used previously may provide equivalent benefits. Previous studies of higher dose ICS (as in the TORCH study[7]) provided impetus for the tendency to treat all patients with higher doses as these doses were used both in the TORCH study and in other trials (1000 mcg daily fluticasone propionate). However, the TORCH trial not only demonstrated a beneficial effect of an inhaled LABA/ICS combination in reducing exacerbations but also provided the initial signal that ICS use can be associated with excess cases of pneumonia in patients with COPD; this has been a consistent finding in

subsequent studies.[8,10,11] Lower doses of ICS may provide an improved benefit-to-risk profile and future studies using lower doses of ICS in COPD are therefore crucial.

What about triple therapy?

Current guidelines recommend that consideration should be given to adding ICS in a stepwise fashion in patients with COPD who continue to have exacerbations or who are symptomatic despite dual bronchodilator therapy.[1] Currently, this approach means changing from a LAMA/LABA combination to a LABA/ICS combination plus a separate LAMA. The addition of an all-in-one ICS/LABA/LAMA to the COPD treatment armamentarium may simplify therapy and could reduce out-of-pocket expenses for those patients who merit maximal therapy. To date there have been no comparisons of one form of triple therapy with another.

The development of pneumonia in patients using ICS remains a vexing issue, so selection of therapy must be based on the best choice for that patient, perhaps employing a shared responsibility approach. This would entail discussing benefits and risks for that particular person. Factors to consider are exacerbation history, low body weight, presence of osteoporosis, history of side effects on ICS and whether alternative options – such as pulmonary rehabilitation – have been fully explored.

One other feature of COPD requires consideration. Post-hoc and retrospective studies have suggested that a blood eosinophil count may be a useful biomarker to determine the likelihood of a response to ICS.[13] Although the FLAME study did not detect a predictive response to ICS based on measured eosinophil count, the IMPACT study found a greater benefit in patients with higher eosinophil counts. This measure may thus be a useful biomarker in future, and further prospective studies are awaited.

The bottom line

A stepwise approach to therapy is appropriate. COPD-X guidelines suggest initial treatment with a short-acting bronchodilator for a patient with COPD who is minimally symptomatic, increasing to a single long-acting bronchodilator for those with more symptoms.[1] Combination LAMA/LABA bronchodilator therapy is appropriate for patients whose symptoms are still inadequately controlled and who have repeated exacerbations, defined as a change in the patient's baseline dyspnoea, cough and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication or hospital admission.[1] If the patient's symptoms and exacerbations are still not adequately controlled the next step may be triple therapy – with two inhalers or, stepping up to an 'all-in-one' triple-therapy inhaler which will be available in Australia from June 2018.

Importantly, management of COPD involves much more than pharmacological therapy. All patients should be encouraged to be physically active, should be referred to a pulmonary rehabilitation program (https://lungfoundation.com.au/health-professionals/ clinical-resources/pulmonary-rehabilitation-resources) and need to be up to date with influenza and pneumococcal vaccinations. Identification and treatment of comorbidities such as cardiac disease, osteoporosis, depression and anxiety, and gastro-oesophageal reflux disease as well as coexistent asthma may have substantial benefits on symptoms and exacerbations. For more information about COPD management please refer to https://copdx.org.au. MT

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COMPETING INTERESTS: Professor Bardin has served on advisory boards for Novartis, GlaxoSmithKline, AstraZeneca and Boehringer Ingelheim and has given lectures on their behalf. Professor McDonald has received honoraria for advisory board participation and/or education presentations from Novartis, Menarini, Pfizer and GlaxoSmithKline, and nonfinancial support from Air Liquide, outside the submitted work; and is Chair of the COPD National Program, Lung Foundation Australia.