One Bronchodilator or two?

Author
Dave Singh
Division of Infection, Immunity and Respiratory Medicine, Medicines Evaluation Unit, University Hospital of South Manchester Foundation Trust, University of Manchester

Correspondence
Dave Singh
8 Wenlock Road, Sale, Manchester, m33 3TR, UK
University of Manchester, Manchester, UK
DSingh@meu.org.uk

Chronic obstructive pulmonary disease is characterised by persistent airway obstruction and airway inflammation. The major goals of treatment are to improve symptoms and reduce exacerbations. The cornerstone of the pharmacological management of COPD is maintenance treatment with inhaled long-acting bronchodilators. There are two classes of long-acting bronchodilators: long-acting muscarinic antagonists (LAMAs) and long-acting β2-adrenergic agonists (LABAs). LAMAs target the muscarinic receptors to inhibit the bronchoconstrictor action of acetylcholine, while LABAs promote bronchial smooth muscle relaxation through increased cAMP signalling. These drugs cause bronchodilation, which reduces symptoms and increases exercise capacity. Long acting bronchodilators can also reduce the frequency of exacerbations. The other major class of treatment is inhaled corticosteroids (ICS). These are anti-inflammatory drugs that are used to prevent future exacerbations in those patients at increased risk of exacerbations. The future risk of exacerbations is predicted by the history of exacerbations.

The distinct mechanisms of action of LAMAs and LABAs allows these classes of drugs to be combined to increase the magnitude of bronchodilation compared to monotherapy. LAMA/LABA combination inhalers have been developed which provide significantly greater bronchodilation than monotherapies. Clinical trials with patient reported outcomes (PROs) as the primary endpoint have demonstrated that these dual bronchodilators also significantly improve symptoms and health related quality of life compared to monotherapies. The magnitude of these differences when comparing two bronchodilators against one have been intensely debated, as the mean differences fail to reach the accepted minimal clinically important difference (MCID) thresholds. However, these MCID thresholds are unrealistic when comparing active treatments, and the magnitude of difference observed is likely to be clinically important. This view is supported by positive individual responder analysis of PRO results in favour of two bronchodilators against one. Furthermore, post-hoc analysis using the composite endpoint of clinically important deteriorations shows that two bronchodilators are better at maintaining disease stability.

The data from randomised clinical trials supports the superior overall clinical efficacy of two bronchodilators versus monotherapy. The Global initiative for Obstructive Lung Disease (GOLD) recommends dual bronchodilators as a step up treatment (from monotherapy) for patients in groups B, C and D. In group B patients, GOLD also states that dual bronchodilator treatments can be initiated as first line treatment in more symptomatic patients, but evidence to support this is sparse. For patients with the highest burden of symptoms and exacerbations (group D), dual bronchodilators are the preferred treatment of choice for the newly diagnosed patient. This is based on clinical trials in patients at increased exacerbation risk that have shown superior efficacy of LAMA/LABA versus LAMA monotherapy and versus ICS/LABA for exacerbation reduction.

An unresolved question is the long term benefits of LAMA/LABA treatment in mild to moderate COPD. Do dual bronchodilators reduce disease progression in these patients? If so, should we start all patients on dual bronchodilators? Alternatively, is there a subgroup of patients (e.g. more symptomatic) who derive the greatest benefit from dual bronchodilators? A personalised approach to COPD treatment is advocated by GOLD. Accordingly, we should search for ways of identifying patient subgroups who can be adequately treated with long acting bronchodilator monotherapies, and those who need early intervention with LAMA/LABA combinations.
References


