Chronic obstructive pulmonary disease (COPD): indacaterol/glycopyrronium combination inhaler compared with tiotropium and formoterol in a randomised, non-inferiority study

A 26-week double-blind randomised controlled trial in people with moderate to severe COPD found that indacaterol/glycopyrronium was non-inferior to tiotropium plus formoterol in terms of health related quality of life. Treatment differences in secondary outcomes relating to breathlessness and exacerbations were not statistically significant. This combination of LABA/LAMA may provide another option within the current NICE COPD guidance recommendations, where personalisation of therapy is key.

Overview and current advice

Indacaterol/glycopyrronium (Ultibro Breezhaler) is a once-daily, inhaled long-acting beta-2 agonist (LABA)/long-acting muscarinic receptor antagonist (LAMA) combination inhaler. It is indicated as a maintenance bronchodilator treatment to relieve symptoms in adults with COPD (summary of product characteristics for Ultibro Breezhaler) and was launched in the UK in 2014.

The NICE guideline on COPD makes several recommendations about inhaled treatments for managing stable COPD that are relevant to the likely place in therapy of indacaterol/glycopyrronium. The guideline recommends that people with forced expired volume in 1 second (FEV1) ≥50% predicted who experience exacerbations or persistent breathlessness despite use of a short-acting bronchodilator should be offered either a LAMA or a LABA. People with an FEV1 <50% predicted should be offered either a LABA with an ICS in a combination inhaler or a LAMA. The use of dual therapy with a LAMA and LABA may be considered if an inhaled corticosteroid (ICS; as part of combination therapy with a LABA) is declined or not tolerated, see the NICE guideline for more details.

The NICE evidence summary: new medicine (ESNM33, published February 2014) on indacaterol/glycopyrronium (Ultibro Breezhaler) focused on 2 published studies (SPARK\(^1\) and BLAZE\(^2\)) that reported patient orientated primary outcomes. In SPARK (n=2224), indacaterol/glycopyrronium statistically significantly reduced the rate of moderate to severe exacerbations compared with glycopyrronium alone in people with severe or very severe COPD.
However, the reduction was very small and of uncertain clinical benefit. BLAZE (n=247) found that indacaterol/glycopyrronium produced small statistically significantly improvements in dyspnoea (breathlessness) scores compared with placebo in people with moderate or severe COPD, however, this difference is unlikely to be clinically important.

The NICE pathway on COPD brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A German 26-week multicentre, randomised controlled trial (RCT), with a blinded, parallel-group, triple-dummy design has reported on the non-inferiority of indacaterol/glycopyrronium to tiotropium plus formoterol in improving health related quality of life of people with moderate to severe COPD (n=934). The study population included adults aged 40 years or over (mean age 63 years), people who smoke or used to smoke with a smoking history of at least 10 pack-years and post-bronchodilator FEV1 of 30% or more and less than 80% of predicted value. Exclusion criteria included COPD exacerbation that needed treatment with antibiotics, corticosteroids (oral or intravenous) or hospitalisation in the 6 weeks before pre-screening. People receiving ICS at baseline continued treatment at the same or equivalent dose and regimen. People were randomised to delivered doses of either indacaterol 110 microgram/glycopyrronium 50 microgram combination once daily (n=476) or tiotropium 18 microgram once daily plus formoterol 12 microgram twice daily (n=458). Salbutamol was used as a rescue drug. Baseline population demographics and characteristics were similar across the treatment groups. Allocation was concealed.

The primary outcome was non-inferiority of indacaterol/glycopyrronium compared with tiotropium plus formoterol for health related quality of life, as measured by the shortened version of the St. George’s Respiratory Questionnaire (SGRQ-C). The pre-defined non-inferiority margin was 4 units, the minimum clinically important difference according to the full NICE guideline on COPD. Secondary outcomes included breathlessness score (assessed using the Transition Dyspnoea Index [TDI]), lung function scores (assessed using spirometry), rate of moderate and severe exacerbations and time to first exacerbation.

For the primary outcome, non-inferiority was demonstrated (p<0.001) for indacaterol/glycopyrronium compared with tiotropium plus formoterol as the upper margin of the 95% confidence interval [CI] was lower than the pre-defined non-inferiority margin of 4 units in both the intention-to-treat population (−0.69, 95% CI 2.31 to 0.92) and the per-protocol population (−0.77, 95% CI −2.48 to 0.93). The small treatment difference in favour of indacaterol/glycopyrronium was not statistically significant.

Reduction in breathlessness scores between the 2 treatment groups was not statistically significantly different (treatment difference 0.38, 95% CI 0.06 to 0.82, p value not reported). The percentage of people who had at least 1 moderate or severe exacerbation and time to first moderate or severe exacerbation was comparable between the treatment groups and not statistically significantly different.

Adverse events were comparable in both treatment groups and not statistically significantly different (43.7% and 42.6% for indacaterol/glycopyrronium and tiotropium plus formoterol, respectively [RR 1.03, 95% CI 0.89 to 1.19]). More people in the tiotropium plus formoterol group developed pneumonia (RR 0.12, 95% CI 0.03 to 0.96) and more people in the indacaterol/glycopyrronium group...
had a myocardial infarction but the confidence intervals were very wide (RR 3.85, 95% CI 0.46 to 18.24). The authors state that these results did not highlight any additional safety concerns for indacaterol, glycopyrronium, tiotropium or formoterol.

This study evaluated patient orientated outcomes and the authors state that this is the first study to evaluate health related quality of life as a primary end point for comparing active pharmacological interventions used in COPD. The authors state that a limitation of the study was that it only considered the incidence of at least 1 exacerbation rather than the number of exacerbations experienced during the study period. The majority of the baseline population (86%) had no previous history of COPD exacerbations, which may be a limitation of the results in relation to people with more unstable disease. Further limitations the authors highlight are the potential impact of seasonal variation on disease fluctuations which may have influenced results. In addition, without a placebo arm it is unclear if some improvements were due to better disease management during a clinical trial.

Commentary

Commentary provided by Dr Sarah Scrivener, Consultant Respiratory Physician, Portsmouth Hospitals NHS Trust

The current NICE COPD guideline advises that the use of dual therapy with a LAMA and LABA may be considered if an ICS as part of combination therapy with a LABA is declined or not tolerated. NICE does not give preference to either of these options. An individualised approach to COPD management, where risks and benefits of treatment are considered, is recommended in both NICE guidance and updated Global initiative for Chronic Obstructive Lung Disease guidance (GOLD, published January 2015). For example, based on evidence from published studies highlighting a significantly increased risk of pneumonia with ICS (either alone or in combination with a LABA), the MHRA recommends that ICS should not be used alone in COPD and should be introduced only when COPD progresses to severe disease, in line with NICE guidance. This advice is supported by a more recent Cochrane review on the issue which has previously been discussed in detail in a NICE medicines evidence commentary.

Patient orientated outcomes such as the frequency of exacerbations and the presence of symptoms are important determinants of which therapies to prescribe on an individual basis. In those with moderate disease and infrequent exacerbations there is more emphasis on initially using bronchodilator therapy. It is in this subset of people with COPD that indacaterol/glycopyrronium may be more beneficial. In this study it should be noted that 40-42% of patients were taking ICS and therefore they may not accurately represent the effect of LABA/LAMA combination therapy alone. This study shows non-inferiority of the fixed dose indacaterol/glycopyrronium for health-related quality of life compared with formoterol plus tiotropium, but the study was not designed to demonstrate a treatment difference. The bronchodilation effect of indacaterol/glycopyrronium may account for some of the improvement shown in breathlessness scores and although treatment difference was not statistically significant, on an individual responder basis some symptom improvement may be clinically important. An additional factor to consider is that compared with established drugs such as formoterol, salmeterol and tiotropium, the long-term safety of indacaterol and glycopyrronium (alone or in combination) is still emerging.
The way forward in COPD inhaled therapy seems to be a personalised approach. In people having few exacerbations but who are experiencing lots of symptoms, a combination LABA/LAMA inhaler seems to be an efficacious treatment with less side effects than the addition of ICS. In tune with the “personalisation", the choice of inhaler and frequency of administration are also important. It is generally accepted most people prefer a once-daily treatment and this can improve adherence. Selecting an inhaler device ensuring sufficient inspiratory flow to achieve therapeutic drug deposition, the person’s ability to use the device correctly and their preferences are also important factors for consideration.

Study sponsorship
This randomised controlled trial was supported and funded by Novartis Pharma GmbH, Germany. Writing support was funded by Novartis Pharma AG, Basel, Switzerland.

References

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