Chronic obstructive pulmonary disease (COPD): indacaterol/glycopyrronium compared with salmeterol/fluticasone for reducing exacerbations (the FLAME study)

A 52-week, double-blind, randomised controlled trial (RCT) in people with moderate to severe COPD and a history of exacerbations found that the combination of indacaterol/glycopyrronium was superior to the combination of salmeterol/fluticasone in reducing exacerbations. The annual rate of all exacerbations (mild, moderate or severe) was 11% lower with indacaterol/glycopyrronium compared with salmeterol/fluticasone (3.59 compared with 4.03, p=0.003). The incidence of pneumonia was lower in the indacaterol/glycopyrronium group (3.2% compared with 4.8%, p=0.02). The combination of indacaterol/glycopyrronium may be an option for people with COPD, where personalisation of therapy is key. See the NICE guideline on COPD for more information.

Overview and current advice

The NICE guideline on chronic obstructive pulmonary disease which is being updated (publication date to be confirmed) recommends the following inhaled maintenance therapy for people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as needed:

- either a long-acting beta-2 agonist (LABA) or a long-acting muscarinic antagonist (LAMA) if forced expired volume in 1 second (FEV1) is 50% predicted or more
- either a LABA plus an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA if FEV1 is less than 50% predicted.

For people with an FEV1 of 50% predicted or more who remain breathless or have exacerbations despite maintenance therapy with a LABA, a LABA plus an ICS in a combination inhaler or the addition of a LAMA to a LABA (where an ICS is declined or not tolerated) can be considered.

Triple therapy with a LAMA, a LABA and an ICS is an option for people who remain breathless or have exacerbations despite maintenance therapy with either a LABA plus an ICS, or a LAMA, irrespective of their FEV1. The choice of medicine(s) should take into account the person's symptomatic response and preference, and the medicine's potential to reduce exacerbations, its side effects and its cost.

In the study reviewed here, a combination of a LABA plus a LAMA (indacaterol/glycopyrronium) was compared with a LABA plus an ICS (salmeterol/fluticasone) in people with moderate to severe COPD.
who had a history of exacerbations. See the NICE evidence summary on indacaterol/glycopyrronium (Ultibro Breezhaler) for more information on this inhaler. No previous studies have evaluated the efficacy and safety of LABA/LAMA combinations compared with LABA/ICS combinations in people with a history of COPD exacerbations for patient orientated outcomes.

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

The FLAME trial was a multicentre, 52-week, randomised, double-blind, double-dummy, non-inferiority trial comparing indacaterol/glycopyrronium (Ultibro Breezhaler) with salmeterol/fluticasone (Seretide Accuhaler) conducted in 356 centres in 43 counties. In total, 5328 people aged 40 years or older with moderate to severe COPD (grade 2 or higher on the Medical Research Council breathlessness scale), an FEV1 of at least 25% to less than 60%, an FEV1 to forced vital capacity (FVC) of less than 0.70, and a history of at least 1 exacerbation during the previous year which required treatment were screened for inclusion. Following a 1-week screening period to assess eligibility and discontinue prior LABA, LAMA and ICS treatment, and a 4-week run-in period where all participants received inhaled tiotropium, tiotropium was discontinued and 3362 people were randomised (allocation was concealed). Participants were randomised to indacaterol/glycopyrronium (110/50 micrograms) once daily (n=1,680) or salmeterol/fluticasone (50/500 micrograms) twice daily (n=1,682) for 52 weeks. Salbutamol was available as a rescue medicine.

Baseline characteristics were similar in both groups. In all participants the time from diagnosis of COPD was about 7 years, 40% were current smokers, average FEV1 was 44.1±9.5% of predicted, the St. George’s Respiratory Questionnaire for COPD (SGRQ-C) score was 47.3±15.8, 19% had a history of 2 or more exacerbations during the previous year, and 56% were using ICS at the time of screening. Discontinuation rates were 17% in the indacaterol/glycopyrronium group and 19% in the salmeterol/fluticasone group.

The primary outcome was the annual rate of all (mild, moderate or severe) COPD exacerbations. In the per-protocol population (n=3084), the annual rate of all COPD exacerbations was 3.59 (95% confidence interval [CI] 3.28 to 3.94) in the indacaterol/glycopyrronium group and 4.03 (95% CI 3.68 to 4.41) in the salmeterol/fluticasone group. This was a statistically significant 11% lower rate in the indacaterol/glycopyrronium group (rate ratio 0.89, 95% CI 0.83 to 0.96; p=0.003). The upper limit of the 95% CI for the rate ratio was less than 1.15 (the non-inferiority margin) therefore indacaterol/glycopyrronium was non-inferior to salmeterol/fluticasone for this outcome. It was also less than 1, so indacaterol/glycopyrronium was superior to salmeterol/fluticasone for this outcome (superiority could be tested for if non-inferiority was established). These non-inferiority and superiority results were based on the rate of all exacerbations, and were confirmed in the modified intention to treat population (n=3354).

There were 27 secondary outcome measures in this trial, 19 of which were reported in the paper. These included time to first exacerbation, annual rate of moderate or severe COPD exacerbations (defined as exacerbations that required the use of health care services), health related quality of life (measured by SGRQ-C score), and the change from baseline in trough FEV1. The safety of indacaterol/glycopyrronium and salmeterol/fluticasone was also assessed.

The time to first exacerbation (mild, moderate or severe) was longer in the indacaterol/glycopyrronium group than in the salmeterol/fluticasone group (median 71 days compared with 51 days; hazard ratio [HR] 0.84, 95% CI 0.78 to 0.91; p<0.001). The time to the first moderate or severe exacerbation (HR 0.78, 95% CI 0.70 to 0.86; p<0.001) and the first severe exacerbation (HR 0.81, 95% CI 0.66 to 1.00; p=0.046) were also longer in the indacaterol/glycopyrronium group. The annual rate of moderate or
severe exacerbations was 0.98 in the indacaterol/glycopyrronium group and 1.19 in the salmeterol/fluticasone group (a statistically significant 17% lower rate; rate ratio 0.83; 95% CI 0.75 to 0.91; p<0.001).

At week 52, there was a between group difference of −1.8 (p<0.01) on the 100-point SGRQ-C score favouring indacaterol/glycopyrronium. The percentage of participants whose SGRQ-C score improved by at least 4 points (the minimal clinically important difference) was also higher in the indacaterol/glycopyrronium group than in the salmeterol/fluticasone group (49.2% compared with 43.7%, p<0.001).

The incidence of adverse events, including serious adverse events and deaths, was similar in the 2 groups. A total of 24 participants in each group (1.4%) died; the most common causes of death were respiratory and cardiovascular causes. The incidence of pneumonia was lower in the indacaterol/glycopyrronium group compared with the salmeterol/fluticasone group (3.2% compared with 4.8%; p=0.02).

The FLAME trial was a large RCT that compared and evaluated the efficacy and safety of a LABA/LAMA regimen with a LABA/ICS regimen based on patient oriented outcomes such as exacerbations, health related quality of life and adverse events. However, it does have limitations. The authors state that because some participants who were treated with a LABA/ICS regimen before enrolment were then assigned to a LABA/LAMA inhaler, they may have had withdrawal effects from the long-term use of their previous regimen, which could have resulted in increased exacerbations. Also, during the run-in period, people were given tiotropium which could have favoured inclusion in the trial of people who tolerated or responded to treatment with a LAMA (over 30% of people discontinued during the run-in phase and were not randomised). It is also reported in the paper that because mild exacerbations were the most common events seen in the trial, this could have made non-inferiority for the primary outcome more likely; assuming a lack of difference between treatments for mild exacerbations. However, the indacaterol/glycopyrronium group had lower rates of both mild exacerbations and moderate and severe exacerbations combined. As with controlled studies generally, it is also unclear if some improvements were due to better disease management during a clinical trial and if similar benefits would be realised in real world clinical practice.

Commentary
Commentary provided by Dr Anastasios Lekkas, FRCP, Consultant Respiratory Physician, University Hospital of Southampton

The current NICE guideline on COPD advises that the use of dual therapy with a LAMA and LABA may be considered for people with an FEV1 of 50% predicted or more who remain breathless or have exacerbations if an ICS as part of combination therapy with a LABA is declined or not tolerated. 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.

The FLAME trial is a comprehensive RCT with some interesting results. Patient oriented outcomes such as the rate of exacerbations and health related quality of life are important when considering which medicines to prescribe on an individual basis. In people with moderate disease and infrequent exacerbations there is more emphasis on initially using bronchodilator therapy with a LAMA or LABA. It is in this subset of people with COPD that a combination of a LABA plus a LAMA may be more beneficial. This study shows non-inferiority of indacaterol/glycopyrronium for the annual rate of all COPD exacerbations compared with salmeterol/fluticasone, and also demonstrated superiority for
indacaterol/glycopyrronium. The bronchodilation effect of indacaterol/glycopyrronium may account for some of the improvement shown in quality of life scores and, on an individual basis, some symptom improvements may be clinically important.

However the study has some limitations and the results need to be interpreted with caution. For example, about 25% of participants recruited to each arm were defined as Group B on the Global initiative for Chronic Obstructive Lung Disease (GOLD) staging system (low risk of exacerbations and high symptom burden) and 75% as Group D (high risk of exacerbations and high symptom burden). People with low symptom burden but high risk of exacerbations (Group C) were not included. Additionally, certain groups of people were excluded from the study such as those with severe co-existing co-morbidities or those with a history of asthma. A proportion of people with COPD have asthma-COPD overlap syndrome where treatment with ICS is helpful, hence people should be screened for this before any change in current recommended treatment is implemented. It is not clear if the results from the FLAME trial would be replicated in a different patient population, for example in people experiencing more frequent or more severe exacerbations (only 19% of people had a history of 2 or more exacerbations in the FLAME trial, and most exacerbations were mild), in people with low symptom burden but high risk of exacerbations, in people with existing co-morbidities, or in people who had not already been selected based on a 4-week LAMA run-in period. The accompanying editorial discusses concerns over switching people from a LABA/ICS regimen to a LABA/LAMA regimen, and the resultant withdrawal of ICS.

An individualised approach to COPD management, where the risks and benefits of treatment are considered, is recommended in both NICE and GOLD guidance. In people having few exacerbations but who are experiencing lots of symptoms, a combination LABA/LAMA inhaler seems to be an efficacious treatment with fewer side effects than the addition of ICS (in particular, a lower risk of developing pneumonia). However, as pointed out in the study and the accompanying editorial, more trials of longer duration comparing other LABA/LAMA combination inhalers with LABA/ICS combination inhalers are required to confirm these findings and to establish if the observed difference in exacerbations is due to a class effect and not related to the specific LABA/LAMA combination studied in the FLAME trial.

The comparative treatment costs of LABA/LAMA and LABA/ICS are similar at around £30-40 per month⁴. The choice of inhaler and frequency of administration are important factors to consider on an individual basis. However, it is generally accepted that most people prefer a once-daily treatment, such as a LABA/LAMA regimen which may improve adherence compared with a twice daily LABA/ICS regimen. Other important considerations are the person’s preferences, selecting an inhaler device that ensures sufficient inspiratory flow to achieve therapeutic drug deposition and the person’s ability to use the device correctly.

Study sponsorship
This RCT was sponsored by Novartis Pharmaceuticals, the manufacturer of indacaterol/glycopyrronium (Ultibro Breezhaler).

References
4. Costs taken from the Drug Tariff (October 2016) where available or alternatively MIMS (October 2016). All costs include the inhaler device
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