Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 1 – June 2017

COPD: New Cochrane review compares LAMA+LABA and LABA+ICS

In recent years, combination dual bronchodilator inhalers containing a long-acting beta-agonist plus a long-acting muscarinic antagonist (LABA+LAMA) have become available for the management of chronic obstructive pulmonary disease (COPD). Some guidelines are now recommending them in preference to LABA plus inhaled corticosteroid (LABA+ICS) therapy. A new Cochrane review seems to support the evolving place of LAMA+LABA inhalers in the management of COPD, finding reductions in exacerbations and risk of pneumonia, improvements in lung function and benefits in some quality of life measures with LABA+LAMA compared with LABA+ICS. The evidence is still of relative poor quality (*graded as low or moderate in this Cochrane review*), so regular review of people with COPD is essential to ensure they are responding to treatments, stopping them if necessary and switching to other treatments within the care pathway.

Ref: Horita N, Goto A, Shibata Y *et al*. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD012066.

What do we know already?

- LABA+LAMA dual bronchodilator inhalers were first launched in 2014 for the treatment of COPD. There are now 4 available: Anoro Ellipta (vilanterol+umeclidinium), Duaklir Genuair (formoterol+aclidinium), Spiolto Respimat (olodaterol+tiotropium) and Ultibro Breezhaler (indacaterol+glycopyrronium).
- NICE guidance on COPD, which was published 2010 before the availability of LABA+LAMA combination inhalers, recommends LABA+LAMA as an option to be considered only when an LABA+ICS is declined or not tolerated. However, in recent years, there has been debate about the relative benefits of long-term ICS use in COPD, as explored in the 2015 WISDOM study. Also, there is also a growing body of evidence for LABA+LAMA inhalers. The NICE guideline is currently being updated, with a publication date of November 2018.
- The latest (2017) update to the GOLD COPD guideline recommends stepping up to a combination LABA+LAMA as first-choice combination therapy when initial treatment with a single long-acting bronchodilator is insufficient for patients graded as B, C or D (i.e. high risk of exacerbations or high symptom impact scores). Like NICE, GOLD now also recommends de-escalation of treatment where the introduction of additional inhaled therapy has not improved symptoms. See GOLD 2017 for the full advice. (*A previous Keele/ScriptSwitch Rapid Update has also discussed the 2017 update to GOLD [user registration required]*).

What does this evidence add?

- This new Cochrane systematic review provides further analysis of the potential benefits and risk of harms with LABA+LAMAs, as a class, versus LABA+ICS for COPD. The review identified 11 trials for inclusion that had mostly recruited participants with moderate to severe COPD, with follow-up ranging from 6 to 52 weeks. In all studies LABA+ICS treatment was with salmeterol plus fluticasone propionate.
- Although some differences were quite small, and findings were based on low-to-moderate quality evidence, there were benefits for LAMA+LABA therapy over LABA+ICS for some important outcomes, including:
  - fewer exacerbations (odds ratio [OR] 0.82, 95% Confidence Interval (CI): 0.70-0.96 in the pooled analysis)
  - a larger improvement in trough forced expiration in 1 second (FEV_1) (mean difference [MD] was 0.08 L)
  - a lower probability of pneumonia (OR 0.57, 95% CI: 0.42-0.79)
  - more frequent clinically important improvements in quality of life
- Limitations included differences in the type of exacerbations measured across studies (which the authors overcame by using a broad exacerbation outcome that included events of any severity), lack of long-term follow-up data, heterogeneous study designs and the inclusion of some patients with milder COPD in whom LABA+ICS would not be recommended. Some larger studies and specific LAMA+LABA combinations may have driven the findings of this review, for example the largest study was the 52-week FLAME study of indacaterol/glycopyrronium (*previously summarised in a June 2016 Rapid Update*). However, overall these findings appear to support the updated GOLD guideline.

Review details

The review aimed to compare treatment with LAMA+LABA versus LABA+ICS in people with stable COPD. RCTs of at least one month's duration were included. The review included 11 trials, with 9,839 participants (median 700 per study, range 46 to 3,362). Ten of the studies were double-blind and two had a cross-over design. One study, the FLAME study of indacaterol/glycopyrronium, lasted for 52 weeks, while other studies ranged from 6 to 26 weeks.

Participants:

- All studies recruited adults with a diagnosis of COPD according to GOLD 2016, which was mostly of moderate severity. All except one study included patients without recent exacerbations; the remaining study (FLAME), included only people with a recent exacerbation. FLAME was also the largest trial, accounting for 37% of the total review population.
- Most of the population were men (median 72%, range 65% to 91%). The mean age reported across the studies was 61 to 71 years, median mean 63 years).

Intervention and comparison:

- Treatment with LAMA+LABA was compared with LABA+ICS. The drugs could be administered by a single or two separate inhaler devices. In all the included studies, LABA+LAMA was administered by a single device. The LABA+ICS combination investigated in all studies was salmeterol/fluticasone propionate, administered via a single inhaler in all but one study.
- The dose of salmeterol/fluticasone propionate was 50/250 µg twice daily in 4 studies, and 50/500 µg twice daily in 8 studies, with one study evaluating both doses. The LAMA+LABA combinations and doses evaluated were:
  - indacaterol/glycopyrronium 110/50 µg once daily (3 studies, which comprised 47% of the total population)
  - umeclidinium/vilanterol 62.5/25 µg once daily (3 studies)
  - aclidinium/formoterol 400/12µg twice daily (1 study).
  - tiotropium with: olodaterol (2.5/5 µg or 5/5 µg once daily [2 dosage arms]); indacaterol (18/150 µg once daily); salmeterol (18/50 µg twice daily); formoterol (18/24 µg twice daily) (1 study each).

Outcomes and results:

- *Note that the quality of the evidence for the following outcomes was graded as low or moderate by the reviewers (GRADE criteria).*
- Based on pooled populations, the proportion of patients with **one or more exacerbations** was lower in the LAMA+LABA group (35.0%) compared with the LABA+ICS group (37.7%) (OR 0.82, 95% CI:0.70-0.96; p=0.01; 9 studies evaluated this outcome, n = 8,932.) Of the subgroup analyses to compare the different LAMA+LABA combinations, only participants treated with indacaterol/glycopyrronium had significantly fewer exacerbations compared with LABA+ICS-treated participants (OR 0.72, 95% CI:0.63-0.83, p < 0.001). Hospitalisations for COPD exacerbations were not reported across the included studies.
- The incidence of **serious adverse events** (not defined) in the pooled population was not statistically significantly different between the LAMA+LABA (8.8%) and LABA+ICS (9.6%) groups (OR 0.91, 95% CI:0.79-1.05; p=0.18. (10 studies provided data for this outcome, n = 9,793.)
- The difference between LAMA+LABA and LABA+ICS groups in changes from baseline in the **St. George's Respiratory Questionnaire (SGRQ) total score** was not statistically significant (mean difference [MD] -1.22 (95% CI:-2.52 to 0.07, p = 0.06). Subgroup analysis showed a significant difference in favour of indacaterol/glycopyrronium and 'other LAMA+LABA inhalers' (aclidinium/formoterol and all tiotropium combinations) compared with LABA+ICS (6 studies, n = 5,858.) Significant heterogeneity was observed for this outcome.
- There was a greater increase in trough FEV_1 value from baseline with LAMA+LABA *vs.* LABA+ICS (MD 0.08 L, 95% CI:0.06-0.09, p < 0.0001). The authors comment this MD was greater than the MCID of 0.05 L. Subgroup analyses were in favour of all LAMA+LABA combinations *vs.* LABA+ICS. (6 studies, n = 7,277.)
- Findings for the secondary outcomes of the systematic review were as follows:
  - X-ray-confirmed pneumonia (8 studies n = 8,540): there was reduced risk of pneumonia with LAMA+LABA, with 1.4% of participants in the pooled population experiencing ≥1 episode of pneumonia compared with 2.6% with LABA+ICS (OR 0.57, 95% CI:0.42-0.79; p = 0.0006).
  - all-cause mortality (8 studies n = 8,200): there was a similar risk with both treatments (OR 1.01, 95% CI:0.61-1.67, p = 0.88).
  - total score change of ≥4 points (*considered to be the MCID*) from baseline SGRQ (2 studies with 24 to 52 weeks of observation, n = 3,192): this change was reported for significantly more patients treated with LAMA+LABA (in 50.0% of the pooled population) *vs.* LABA+ICS (44.5%) (OR 1.25, 95% CI:1.09-1.44, p = 0.002).

Level of evidence: Level 2 according to the SORT criteria.

Study funding: Grants from the National Center for Child Health and Development, Japan and the Japan Agency for Medical Research and Development. All but one of the included studies sponsored by pharmaceutical companies.