Not quite a breath of fresh air

Use of combination inhalers in COPD

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We have concerns about the clinical importance of the recommendations and of the evidence for the use of long-acting β-agonist (LABA) and inhaled corticosteroid (ICS) combination inhalers presented in the 2007 update of the Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease (COPD)[1]:

> [T]he combination of SALM/FP [salmeterol-fluticasone] was associated with a reduction in key inflammatory cells and some markers of airway inflammation in mucosal biopsies of COPD patients compared with placebo.[1]

While the "biological rationale" for use of LABA-ICS combination inhalers might provide insight into a possible mechanism of action, reducing the surrogate end point of mucosal inflammation might be of minimal clinical importance. Although there is little debate that clinical status deteriorates as airway inflammation increases, we must ask the following question: does this reduction in mucosal inflammation with the use of LABA-ICS combination inhalers lead to an improvement in clinical status? That is, does the relationship hold in reverse? The lack of correlation and validation of this surrogate marker to relevant clinical end points, such as frequency of exacerbations or mortality, should be emphasized and discussed rather than provided as a basis for clinical decision making.

This leads us into our second comment regarding exacerbation frequency and health status, based on the guideline excerpt below referring to the TORCH (TOwards a Revolution in COPD Health) trial[2]:

> More importantly, treatment with SALM/FP statistically reduced exacerbation frequency, improved lung function and improved health status compared with SALM or FP alone.[1]

The TORCH trial compared LABA-ICS combination therapy with placebo and ICS or LABA alone. In this trial, 34% to 44% of randomized participants withdrew from the study and only exacerbations for those who remained were counted.[2,3] Participants withdrew from the various groups at different rates (and for different reasons).[2,3] Therefore, one cannot assume that the treatment arms were balanced when only participants who stayed in the trial were accounted for. As such, differences in rates of exacerbation among the groups cannot be attributed solely to differences in allocated treatment; rather, the differences might be the result of confounding factors.

Clinical versus statistical significance

Readers must interpret annualized rates of exacerbations and subsequent reductions with caution.[3] In the TORCH trial, the annual rate of exacerbation at baseline was approximately 1 per year.[2] After treatment, LABA-alone patients had a rate of 0.97 per year and LABA-ICS patients had a rate of 0.85 per year.[2] The clinical significance of a statistical reduction of 0.12 exacerbations per year is unclear. Does this mean you would need to treat a patient for 8 years with LABA-ICS combination therapy to prevent one additional exacerbation versus LABA alone? This result is reported as a 12% relative risk reduction in a recent Cochrane review, which is misleading.[2,3]

We are also concerned about the emphasis in the guideline that there is a clinical benefit with LABA-ICS combination therapy versus LABA alone with respect to health status. Nannini et al report a St George's Respiratory Questionnaire (SGRQ) score improvement of -1.64 points (95% CI -2.28 to -1) in 4 studies (N=4700).[3-5] However, the minimum clinically important difference in SGRQ is thought to be a change of at least 4 points.[5] In our opinion, clinicians should be alerted to the fact that trials might have shown a statistical improvement in SGRQ scores with LABA-ICS combination therapy, but this difference might not be clinically perceptible. Again, owing to differential rates of withdrawal, statistical differences in SGRQ scores (health status) could be the result of confounding factors and might be unrelated to the intervention. Furthermore, even if there is a statistical difference in SGRQ scores between patients receiving LABA-ICS combination therapy versus those receiving LABA alone, there is insufficient evidence to support a clinically important change in health status.[3]

A Cochrane systematic review[3] highlights the contribution of the TORCH trial and an earlier trial, TRISTAN

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(TRial of Inhaled STeroids ANd long-acting β_2 agonists),[4] which had similar results to TORCH, to the overall body of evidence for the use of LABA-ICS combination inhalers in COPD patients. These trials accounted for 70% of the overall weighting of the 5 included trials for the outcomes of exacerbation frequency and health status.[2-4] Therefore, we should be examining the outcomes and the authors' analysis of the outcomes used in these particular trials with careful scrutiny.

The guidelines[1] state the following regarding the use of LABA-ICS therapy in combination with tiotropium[6]:

> For patients with moderate to severe COPD with persistent symptoms and a history of exacerbations ... a combination of tiotropium plus a LABA and ICS therapy product ... is recommended to improve bronchodilation and lung deflation, to reduce the frequency and severity of exacerbations and to improve health status.[1]

We assume that the Optimal trial[6] data provide the basis for these guideline recommendations. The Optimal trial studied the addition of LABA-ICS combination therapy, LABA, or placebo to patients who were receiving tiotropium.[6] The authors concluded that "the addition of fluticasone-salmeterol to tiotropium therapy did not statistically influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD."[6]

The aforementioned issues regarding clinically versus statistically significant differences, as well as the lack of accountability of outcomes for patients who withdrew, also apply to interpretation of the Optimal trial. The recommendation from the guideline above is incorrect, as the Optimal trial did not show a significant difference in the frequency and severity of exacerbations among any of the treatment arms.[6] Also, it appears LABA-ICS combination therapy added to tiotropium improves health status more than placebo plus tiotropium (-4.1 points on the SGRQ).[6] However, this analysis is difficult to interpret given the number of patients who were not evaluated for this outcome at week 52, the lack of confidence intervals around the change in SGRQ scores for each treatment arm, and the fact that there did not appear to be a clinically important difference when comparing all other treatment arms.[4]

Bottom line

Clinical practice guidelines are an essential resource for front-line clinicians. However, in order for "bottom line" guideline recommendations to have a positive effect on patient care, we must ensure that these recommendations are based on clinically, rather than statistically, meaningful differences in outcomes.

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Competing interests
None declared

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References

1. O'Donnell D, Aaron S, Bourbeau J, Hernandez P, Marciniuk DD, Balter M, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease—2007 update. *Can Respir J* 2007;14 Suppl B:5B-32B.
2. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356(8):775-89.
3. Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonist for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007;(4):CD006829.
4. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial. *Lancet* 2003;361(9356):449-56. Erratum in: *Lancet* 2003;361(9369):1660.
5. Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax* 2001;56(11):880-7.
6. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease (a randomized trial). *Ann Intern Med* 2007;146(8):545-55. Epub 2007 Feb 19.