COPD: Inhaled Therapy Strategies

In this Issue...

Chronic obstructive pulmonary disease (COPD) continues to be a leading cause of death in the world. COPD is also punctuated by periods of acute worsening of disease (exacerbations), which lead to worse prognosis and quality of life, as well as higher health care costs. Inhaled bronchodilator and corticosteroid therapy have been the mainstay of treatment for the prevention of exacerbations; however, the most appropriate combination of inhaled therapy to maximize benefit and reduce adverse effects has been less clear.

In this issue Dr. Nadia Hansel from Johns Hopkins University School of Medicine reviews recent key publications that support the current GOLD recommendations for managing patients with symptomatic COPD and a history of exacerbations.

**LEARNING OBJECTIVES**

- Discuss the evidence for the preferred treatment strategy for patients with GOLD grade C and D COPD (history of ≥ 2 exacerbations or ≥ 1 exacerbation leading to hospitalization in the previous year).
- Recognize the benefit of ICS therapy in addition to LABA or LAMA therapy in preventing exacerbations.
- Identify the role of supplemental oxygen therapy in patients with moderate resting desaturation or exercise-induced desaturation.

**GUEST AUTHOR OF THE MONTH**

**Commentary & Reviews**

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**Guest Faculty Disclosure**

Dr. Hansel has indicated that she has received a gift in kind from Austin Air and consulting fees from GlaxoSmithKline; and performed contracted research from AstraZeneca and Boehringer Ingelheim Vetmedica GmbH.

**Unlabeled/Unapproved uses**

She has indicated that there will be no references to unlabeled or unapproved uses of drugs or products.

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COMMENTARY

Preventing and treating exacerbations has been a key goal in managing COPD. However, until recently, there has been a lack of direct evidence guiding therapeutic strategy for managing patients with high exacerbation risk (GOLD C and D patients). In particular, recent studies have focused on determining the optimal management for COPD patients with GOLD D1 disease, which includes patients with symptomatic disease (CAT score > 10 or MRC > 2) and a history of COPD exacerbation in the previous year. The most recently updated GOLD guidelines of 2018 recommend LABA/LAMA or ICS/LABA/LAMA as preferred treatments. The studies highlighted in the accompanying reviews provide additional evidence for the current guideline recommendations.

The highlighted studies suggest that LABA/LAMA therapy with or without ICS is better than ICS/LABA or monotherapy with LABA or LAMA alone for preventing exacerbations. The FLAME and TRILOGY trials showed that either LABA/LAMA therapy or ICS/LABA/LAMA were superior to ICS/LABA. Specifically, results of the study by Wedzicha et al (FLAME Trial) showed a 17% reduction in the rate of moderate to severe COPD exacerbations with LABA/LAMA therapy as compared to ICS/LABA. In addition, the TRILOGY Trial by Singh et al showed that treatment with triple therapy (ICS/LABA/LAMA) was associated with a reduction in the rate of moderate to severe exacerbations of 23% compared to those treated with ICS/LABA alone, suggesting that adding LAMA to LABA or ICS/LABA provides additional exacerbation risk reduction.

It is also common in clinical practice for symptomatic patients with COPD to be treated with LAMA alone. The Vestbo et al (TRINITY Trial) suggests that patients with exacerbations may benefit from triple therapy, as triple therapy (ICS/LABA/LAMA) resulted in a 20% reduction in the rate of moderate to severe exacerbations, and compared with LAMA alone, a 32% reduction in the rate of severe exacerbations. Thus, these study results all support the recommendation by GOLD that LABA/LAMA or ICS/LABA/LAMA should be considered first-line therapy for patients with COPD who are symptomatic and at risk of exacerbations (defined as history of > 2 exacerbations or > 1 exacerbation leading to hospitalization in the previous year). Importantly, these studies did not address whether escalation to triple therapy from LABA/LAMA therapy had any additional benefit.

Bottom line: patients at risk for AE-COPD should all get dual long-acting BD (LABA and LAMA). Also, it is acceptable to start people on an ICS in addition to these agents. But until the TRIBUTE trial, we had not known what happens when one is on LABA/LAMA and the ICS is then added.

Recently, Papi et al published results of the TRIBUTE trial, which sought to determine whether escalation to single-inhaler triple therapy (ICS/LABA/LAMA) led to improved COPD outcomes compared with single-inhaler LABA/LAMA therapy. Patients receiving triple therapy had a 15% reduction in adjusted rate of moderate to severe COPD exacerbations compared to dual bronchodilator (LABA/LAMA) group, suggesting that triple therapy is superior to dual therapy for preventing COPD exacerbations.

The identification of subgroups that may receive larger benefit from specific therapies raises the important goal of aiming for personalized therapy for COPD. Several studies suggest that...
not all patients with COPD respond similarly to a therapeutic agent. Therefore, current GOLD guidelines recommend clinicians consider roflumilast in patients with chronic bronchitis who continue to have exacerbations on triple inhaler therapy,\(^2,4\) as this subgroup had improved response to therapy. Further, chronic macrolide therapy can be considered for those with continued exacerbations despite inhaler therapy. Post hoc analyses suggest that macrolides may be more effective among people who no longer actively smoke than in those that continue to smoke.\(^5\) Peripheral eosinophil levels have recently received increased attention in post hoc analyses, as previous studies have suggested that eosinophil counts may predict response to ICS.\(^6\) In the prespecified subgroup analyses of the recent TRIBUTE Trial, those with peripheral eosinophils greater than 2% appeared to be more responsive to adding ICS to LABA/LAMA. However, whether eosinophil counts can be used to guide therapy remains a question, and the optimum cutoff for blood eosinophils to guide therapy is unclear.

Two phase 3, randomized, placebo-controlled, double-blind, parallel-group trials compared mepolizumab, a humanized monoclonal antibody that blocks interleukin-5, with placebo in patients with COPD who had histories of exacerbation while taking triple-inhaler maintenance therapy. In both studies mepolizumab appeared to reduce the mean annual rate of exacerbations among those with an eosinophilic phenotype.\(^7\)

In the METREX study, those with an eosinophilic phenotype had a 18% reduction compared to placebo in adjusted rate of moderate to severe COPD exacerbations if receiving mepolizumab. In METRO, the exacerbations rate was reduced but did not reach statistical significance. However, a greater effect of mepolizumab on the annual rate of exacerbations was found among patients with higher blood eosinophil counts. The increasing availability of biologic therapies that target specific inflammatory pathways, such as mepolizumab, will likely further our ability to provide personalized treatment for COPD in the near future.

References:

It has been established that long-term treatment with supplemental oxygen reduces mortality in patients with severe COPD and resting hypoxemia. Thus, GOLD guidelines recommend that patients with resting oxygen saturation levels below 89% wear supplemental oxygen. However, the effects of oxygen therapy on patients with less severe hypoxemia or hypoxemia solely with exertion have been unclear. The aim of this study was to determine whether COPD patients with moderate resting desaturation (89%-93%) or exercise-induced desaturation (< 90% but ≥ 80% saturation on six-minute walk test) resulted in a composite endpoint of longer time to death or first hospitalization for any cause. In this multicenter, randomized clinical trial, 738 patients were randomized to receive either 1) 24-hour oxygen if resting SpO2 was 89%-93% and oxygen during sleep and exercise if they had desaturation only during exercise, or 2) no supplemental oxygen. In time-to-event analysis, the authors found no significant difference between the trial groups in the composite primary endpoint. The two groups also did not differ in secondary outcomes: all-cause and COPD-related hospitalization rates, or change in quality of life, anxiety, depression, lung function, distance walked in six minutes, or other measures of functional status. The authors concluded, because of the consistency of their findings, that there is no evidence for clinical benefit for patients with COPD who have resting oxygen saturation of more than 88% for long-term supplemental oxygen therapy, regardless of exercise-induced desaturation. It should be noted that the immediate effects of oxygen on symptoms or exercise performance were not assessed and these results do not change the guideline recommendations for oxygen therapy for patients with severe resting hypoxemia.

References:

FLAME: Indacaterol-Glycopyrronium vs Salmeterol-Fluticasone.

Most COPD guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid (ICS), or a long-acting muscarinic antagonist (LAMA) as first-choice treatment for patients with COPD with high risk of exacerbations. However, the role of ICS therapy in COPD has been called into question, and the benefit of a LABA-LAMA regimen without ICS, to prevent exacerbations has been less clear. The authors performed a multicenter, randomized, double-blind, parallel-group, noninferiority trial to investigate whether treatment with LABA-LAMA combination was at least as effective as ICS-LABA therapy for preventing exacerbations. In this study, 3,362 patients with COPD, at least moderate dyspnea, FEV\textsubscript{1} of 25\% to < 60\% predicted and at least one exacerbation in the previous year were randomized to indacaterol 100 mcg and glycopyrronium 50 mcg vs salmeterol 50 mcg and fluticasone 500 mcg. Those randomized to the LABA-LAMA group had few exacerbations (rate ratio 0.89, \(P = .003\)), thus showing noninferiority. The LABA-LAMA group also had longer time to first exacerbation, and lower annual rate of moderate or severe exacerbations. In post hoc analysis, the LABA-LAMA therapy showed reduction in exacerbation rate in both groups with eosinophils < 2\% (rate ratio 0.80, \(P = .004\)) and > 2\% (rate ratio 0.85, \(P = .01\)) compared to ICS-LABA therapy. LABA-LAMA therapy also showed greater improvements in secondary outcomes of FEV\textsubscript{1}, quality of life (SGRQ), and frequency of rescue medication use. The authors conclude that among patients with COPD and a history of exacerbation in the previous year, treatment with indacaterol-glycopyrronium was more effective than salmeterol-fluticasone in exacerbation prevention. This was seen regardless of the baseline peripheral eosinophil count.

TRINITY: Single Inhaler Extrafine Triple Therapy vs Long-Acting Muscarinic Antagonist Therapy.

The authors conducted a long-term study of the effect of single-inhaler triple therapy (ICS/LABA/LAMA) compared to single LAMA therapy as well as open triple (therapy with two inhalers: combination of ICS/LABA inhaler and LAMA inhaler) on the rate of COPD exacerbations. This was a randomized, parallel-group, double-blind, double-dummy, active controlled trial of 2,691 patients with symptomatic COPD with FEV\textsubscript{1} < 50\% and a history of at least one moderate or severe exacerbation in the past year. Patients were randomized in 2:2:1 fashion to fixed triple (beclomethasone dipropionate, formoterol fumarate, glycopyrronium: BDP/FF/GB), LAMA (tiotropium), open triple (BDP/FF + tiotropium). Both fixed triple and open triple were superior to LAMA alone in reducing moderate to severe exacerbations (rate ratio [RR] 0.80, \(P = .0025\) and RR 0.79, \(P = .0095\) respectively). There was no difference in primary outcome between the fixed and open triple-therapy groups. In the subgroup with an eosinophil count of at least 2\%, the reductions in exacerbations were more pronounced (RR 0.70 for fixed and 0.69 for open triple therapy compared to LAMA) than among the lower eosinophil group where the RR were 0.93 and 0.91, respectively, and were not statistically significant. Secondary outcomes with both triple combination therapies showed improved FEV\textsubscript{1} at all time points compared to LAMA alone. At 52 weeks, adjusted mean changes in predose FEV\textsubscript{1} were 0.082 L for fixed triple, 0.085 L for open triple, and 0.021 L for tiotropium, showing superiority of both triple therapies compared to LAMA alone. The authors conclude that fixed- or single-inhaler triple therapy (ICS/LABA/LAMA) results in a 20\% reduction in the rate of moderate to severe exacerbations and a 32\% reduction in the...
rate of severe exacerbations, compared with LAMA alone. There was no clear advantage to the single-inhaler compared with the dual-inhaler therapy for administering ICS/LABA/LAMA combination therapy.

TRILOGY: Single-Inhaler Triple Therapy vs Inhaled Corticosteroid Plus Long-Acting Beta2-Agonist Therapy


Short-term clinical trials have shown that triple therapy with ICS/LABA/LAMA leads to improved symptom control and lung function compared to dual therapy with ICS/LABA; however, when those reports were published, large, long-term clinical trials had not been done to determine whether triple therapy leads to reduced exacerbation rate compared to ICS/LABA. TRILOGY was a randomized, parallel-group, double-blind, active-controlled study aimed to determine whether a single-inhaler formulation of triple therapy (ICS/LABA/LAMA) therapy was comparable to ICS/LABA therapy. 1,368 patients with symptomatic COPD, FEV$_1$ < 50% predicted, and a history of at least one COPD exacerbation in the previous year were randomized to receive either beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide (BDP/FF/GB), or beclomethasone dipropionate and formoterol fumarate (BDP/FF). Three coprimary outcomes were assessed at week 26: change from baseline in predose and two-hour postdose FEV$_1$, and dyspnea (measured by the Transition Dyspnea Index [TDI] focal score, where scores range from -9 to +9 and a positive score shows improvement in dyspnea, with a score of ≥1 representing a clinically significant change). The triple therapy arm (BDP/FF/GB) showed superior pre- and two-hour post dose FEV$_1$ (adjusted mean difference of 0.081 and 0.117 L, respectively; both $P<.001$). The TDI score (dyspnea) improved in both groups (1.71 and 1.50, respectively) without a statistically significant difference between groups; the mean difference between treatment groups was 0.21 units ($P=.21$). In secondary analysis, the adjusted annual rate of moderate to severe exacerbations was lower with BDP/FF/GB compared with BDP/FF (0.41 vs. 0.53; $P=.005$). No association between blood eosinophil concentration and treatment effect was observed. The authors conclude that in patients with COPD who have severe or very severe airflow limitation and an exacerbation history, treatment with triple therapy (ICS/LABA/LAMA) had a greater effect on lung function and rate of moderate to severe exacerbations (23% lower) than those treated with ICS/LABA alone.
TRIBUTE: Extrafine Inhaled Triple Therapy vs Dual Bronchodilator Therapy


TRIBUTE is the first long-term study to compare treatment with single-inhaler triple therapy (ICS/LABA/LAMA) vs single-inhaler LABA/LAMA therapy on the rate of COPD exacerbations. In a randomized, parallel-group, double-blind, double-dummy, active-controlled study, 1,532 patients with symptomatic COPD with FEV₁ < 50% and a history of an exacerbation in the previous 12 months, were randomized to receive either beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide (BDP/FF/G), or indacaterol/glycopyrronium (IND/GLY). The investigators selected IND/GLY as the comparator because it is the only LABA/LAMA combination that has been shown to reduce rate of COPD exacerbations; however, it should be considered that any differences observed between treatment groups could be due to differences in molecules, devices, or the twice-daily vs once-daily dosing regimens. The primary outcome was rate of moderate to severe COPD exacerbations over 52 weeks of treatment.

Over 52 weeks, the rate of moderate to severe COPD exacerbations was lower for patients receive BDP/FF/G compared to IND/GLY (RR of 0.848, \( P = .043 \)), indicating a 15% reduction in the exacerbation rate. COPD subgroups were defined according to the clinical judgment of the investigator; 56% of subjects were determined to have chronic bronchitis, 30% emphysema, and 14% had mixed chronic bronchitis/emphysema. Prespecified subgroup analyses suggested that those with chronic bronchitis (RR 0.752, \( P = .01 \)) but not those with emphysema (RR 0.995; \( P = .974 \)) or mixed bronchitis and emphysema (RR 0.939; \( P = .781 \)) had reductions in exacerbation rate. Similarly, those with peripheral eosinophils ≥ 2% (RR 0.806, \( P = .029 \)), but not those with low eosinophils (RR 0.943, \( P = .685 \)) had an improved response to triple therapy. The authors conclude that the inhaled corticosteroid containing triple combination of extrafine BDP/FF/G in a single inhaler was associated with a lower rate of moderate to severe COPD exacerbations than the dual bronchodilator combination. Secondary analyses suggest that those with a clinical diagnosis of chronic bronchitis or peripheral eosinophils greater than 2% may be more responsive to the addition of ICS.

KEY TAKEAWAYS

- LABA/LAMA or ICS/LABA/LAMA should be considered first-line therapy for patients with COPD who are symptomatic and at risk of exacerbations, and is likely better than bronchodilator monotherapy or ICS/LABA combination.
- Triple therapy (ICS/LABA/LAMA) is likely superior to dual therapy for preventing COPD exacerbations, especially those with a clinical diagnosis of chronic bronchitis and/or peripheral eosinophils greater than 2%.
- While supplemental oxygen has previously been shown to improve survival in COPD patients with marked hypoxia (eg, \( \text{SaO}_2 < 89\% \)), the recent study suggests that it does not improve survival in patients with resting oxygen saturation of 89%-94% or on desaturation (> 80%) with exertion.

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