Symptomatic COPD: Is it time for triple therapy?

Linked commentary - 'Triple combination of budesonide/glycopyrrolate/formoterol fumarate using co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, randomised controlled trial'

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Pharmacological treatment of chronic obstructive pulmonary disease (COPD) aims to improve symptoms and reduce exacerbations[1]. Patients with a higher risk of exacerbations often have more severe airflow limitation and a greater symptom burden. Treatment strategies in this group of high risk patients, who are defined as having significant symptoms (CAT >10) and an exacerbation history (≥2 moderate exacerbations or ≥1 severe exacerbation in past 12 months) advocate the use of dual bronchodilators or an escalation to inhaled corticosteroids (ICS) in combination with dual bronchodilator therapy[1]. The increased risk of pneumonia with ICS in patients with COPD[2] and the apparent limited efficacy of ICS/long-acting beta-2 agonist (LABA) against dual bronchodilators from the FLAME study[3] in addition to the emergent potential of closed triple inhaled combination therapy[4,5] have led concerns surrounding ICS use in patients with COPD. Recent retrospective evaluations aiming to identify patients in whom there is a positive response to ICS have repeatedly shown that peripheral blood eosinophil count may predict ICS response in COPD patients with a past history of exacerbations[6-9]. However, the effect of triple combination inhalers in symptomatic patients without an elevated risk of exacerbations has never been examined and whether peripheral blood eosinophils predict corticosteroid responsiveness in this population is unknown.

In *The Lancet Respiratory Medicine*, Ferguson and colleagues present the results of the KRONOS study[10]. KRONOS[10] examined the effect of closed triple combination inhaled therapy (Budesonide/Glycopyrrolate/Formoterol Fumerate) on lung function and compared this to dual bronchodilator therapy (Glycopyrrolate/Formoterol Fumerate) and ICS combination with long-acting bronchodilator therapy (Budesonide/Formoterol Fumerate) in patients with COPD and a history of symptoms in a 24-week study. Selected patients were symptomatic despite treatment with two or more inhaled treatments, with the majority (approximately 70%) on an ICS-containing compound upon study entry. One important study design feature of KRONOS[10] is included participants did not have to fulfil any exacerbation criteria prior to study entry. In addition

to this, in a pre-specified analysis, KRONOS[10] also prospectively investigated the role of the peripheral blood eosinophil in predicting ICS response in this group of patients.

With respect to the primary findings, unsurprisingly, KRONOS[10] identified that lung function and symptoms were no worse and largely improved in patients randomised to the triple combination inhaled therapy (ICS/LABA/LAMA) compared to dual bronchodilator therapy (LABA/LAMA) or to the ICS combination with long-acting bronchodilator therapy (ICS/LABA). Of the secondary analyses, KRONOS[10] studied the effect of exacerbation in the triple combination inhaled therapy against the dual combination therapy and the ICS combination with long-acting bronchodilator therapy, in a population that were deemed to have a low risk of exacerbations. The authors demonstrated that model-estimated rates of exacerbations (this was a 24 week study) were significantly reduced in the triple combination inhaled therapy compared to the dual bronchodilator therapy groups, with trends but not reaching statistical significance against the ICS combination with long-acting bronchodilator therapy. Although a secondary analysis and a model-adjusted exacerbation rate, the reduction of exacerbations in the triple combination inhaled therapy greater than that of dual bronchodilator therapy is in line from the findings observed in the TRIBUTE[4] and IMPACT[5] studies, further suggesting the this is an effective treatment, with a safe treatment profile.

The KRONOS[10] study also assessed these primary findings with relation to the peripheral blood eosinophil count. KRONOS[10] demonstrated that lung function (trough FEV_1) benefits of the triple combination inhaled therapy against the dual bronchodilator therapy were more pronounced in patients with a peripheral blood eosinophil count greater than 250 cells/mm^3 ; whilst against the ICS/LABA (Budesonide/Formoterol Fumerate) combination this occurred at peripheral blood eosinophil levels over 100 cells/mm^3. Furthermore, at the lower peripheral blood eosinophil level of 100 cells/mm^3 a treatment difference of the triple combination inhaled therapy against the dual bronchodilator therapy for model-adjusted exacerbation rates could be seen. It is interesting to note that largely the treatment effect thresholds between the triple combination inhaled therapy against the dual bronchodilator therapy for exacerbation rate reduction occurred at peripheral blood eosinophil levels which exceeded 100cells/mm^3; a finding more apparent using continuous analyses of the peripheral blood eosinophil count. These ranges are consistent and have corresponded to the treatment interaction effect of ICS/LABA against LABA in past albeit post-hoc studies using similar continuum analyses of the peripheral blood eosinophil count[9]. In the first prospective study examining the effect of peripheral blood eosinophils and inhaled corticosteroid responsiveness using continuous analysis, this threshold of peripheral blood eosinophil level and exacerbation effect suggests robustness of the peripheral blood eosinophil count as a marker to ICS response in patients with COPD; a threshold occurring in approximately 80% of the COPD population. Furthermore, KRONOS[10] adds to the previous continuous analyses[9] to define the robustness of the peripheral blood eosinophil at a cut-off of ≥ 100cells/mm^3 for identifying the ICS responsive COPD patient. The difference in effect for lung

function at the higher peripheral blood eosinophil count between the triple combination inhaled therapy and the dual bronchodilator therapy, is likely as a consequence of the bronchodilator treatment response, i.e. the additional effect of the LAMA in this analysis.

It is important to note that the study design of KRONOS[10] stated that patients had to be symptomatic and on two inhaled therapies for study inclusion prior to randomisation to one of 4 treatment arms. This study design meant that some patients had treatment withdrawn; whilst approximately 70% of the population in the screening phase were on an ICS-containing compound. Although it would appear that the population studied were patients with symptomatic COPD without an exacerbation risk, it is of course conceivable that the majority of the population studied were ICS-responders and that continuation of their ICS treatment is beneficial to reducing their future exacerbation risk. Whether these patients are at a real lower exacerbation risk remains to be determined and further exploration of the magnitude of risk in patients with COPD warrant further investigation. Replication of the KRONOS[10] findings in a 12-month study period will be required and are awaited to reinforce the utility of the peripheral blood eosinophil as a marker of ICS response in COPD and to integrate into guidelines and clinical practice. At present, the mechanism underpinning the role of the eosinophil in COPD is not clear[11] and studies to investigate the mechanistic role of the eosinophil in COPD are required; nevertheless, the findings from KRONOS[10] adds to the current evidence base that highlights that this is a marker of inhaled corticosteroid responsiveness and our patients with symptomatic COPD are likely to have benefit.

References

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