# The Significance of Eosinophilic Inflammation in COPD

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We are responding to the original article by Roche and colleagues (1) and subsequent correspondence (2, 3) about the effects of dual bronchodilator therapy on COPD exacerbations and the potential role of eosinophils in determining the differential benefit over an ICS/LABA combination. Professor Roche and his colleagues reiterate the view that eosinophil counts make no difference in determining this differential response. We feel they are not acknowledging what is actually shown by the data.

Figures 1 and 2 in the original paper (1) clearly demonstrate that the differential benefit, in terms of exacerbation rate ratio and hazard ratio, of dual bronchodilator therapy over an ICS/LABA combination therapy, becomes numerically less with higher eosinophil counts in a convincing step-wise fashion. In addition, there is no statistically significant difference in the rate ratio when the blood eosinophil count exceeds 3% or 150 cells/mcl and no difference in the hazard ratio (which is the most robust exacerbation metric) between the two treatments when the blood eosinophil count exceeds 5% or 300 cells/mcl. Also, it is important to note that in the FLAME study COPD patients with eosinophil levels above 600/µL were excluded, as well as patients with a history of asthma or concomitant allergic rhinitis. We believe that, if these types of patients been included, the influence of eosinophils would have been even more obvious.

Thus, one must conclude that eosinophil count is an important determinant of the relative effectiveness of dual bronchodilator therapy over an ICS/LABA combination therapy in terms of reducing moderate and severe COPD exacerbations. We are not presented wth a breakdown of exacerbation types and are thus not able to determine whether the relationship between treatment efficacy and blood eosinophil count differs for episodes treated with antibiotics alone compared to those treated with oral corticosteroids (OCS) . This is an important omission, as an earlier study (4) showed that OCS

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treated events were more effectively inhibited by ICS/LABA than long-acting antimuscarinic treatment whereas the reverse was true for episodes treated with antibiotics alone.

A final important point is that the conclusions drawn from the FLAME study (5) are being regarded as synonymous with differences in pharmacology. However, clearly the comparison involved different molecules with different devices and different frequency of administration. Without adherence data the comparison is of limited value.

There is now general acceptance, among COPD specialists, that dual bronchodilator therapy has significant and clinically important benefits in reducing exacerbation risk in COPD patients. The FLAME study (5) is undoubtedly a convincing in this regard, but the results are really not surprising. Previously, it had been demonstrated that dual bronchodilators produced greater improvement in pulmonary function compared with ICS/LABA (6), and reduced exacerbation risk is strongly associated with improved $FEV_1$ (7). Therefore, comparing two bronchodilators with a combination therapy that contains only one is not a really a fair comparison. Furthermore, this is not the main point of contention.

No-one is arguing that ICS plus LABA is superior to LAMA plus LABA with regard to reducing exacerbation risk. However, we should acknowledge that ICS/LABA combination therapies also clearly reduce the risk of exacerbations in COPD patients (8) and a wealth of evidence now shows that this benefit is greater with higher eosinophil counts (9, 10). This is exactly the reason why the differential benefit of dual bronchodilator therapy over ICS/LABA reported by Roche, et al (1) is less with higher eosinophil count and actually why there is no difference above certain eosinophil levels.

Moving on from FLAME, let us agree that dual bronchodilator therapy should be regarded as foundational therapy for all symptomatic patients with COPD and that higher eosinophil counts can help identify those patients who are more likely to respond favorably to inhaled corticosteroids (11).

1. Roche N, Chapman KR, Vogelmeier CF, Herth FJF, Thach C, Fogel R, et al. Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. Am J Respir Crit Care Med. 2017;195(9):1189-97.
2. Yilmaz I, Turk M. Correspondence Letter Regarding "Blood Eosinophils and Response to Maintenance COPD Treatment: Data from the FLAME Trial". Am J Respir Crit Care Med 2017; 196:1229-1230
3. Roche N, Chapman KR, Vogelmeier CF, Herth FJF, Thach C, Fogel R, et al. Reply to Correspondence Letter Regarding "Blood Eosinophils and Response to Maintenance COPD Treatment: Data from the FLAME Trial". Am J Respir Crit Care Med 2017; 196:1230-1231
4. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med. 2008;177(1):19-26.
5. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med. 2016;374(23):2222-34.
6. Donohue JF, Worsley S, Zhu CQ, Hardaker L, Church A. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. Respir Med. 2015;109(7):870-81.
7. Zider AD, Wang X, Buhr RG, Sirichana W, Barjaktarevic IZ, Cooper CB. Reduced COPD exacerbation risk correlates with improved FEV1: A meta-regression analysis. Chest. 2017.
8. Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013(11):CD003794.
9. Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, et al. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2015;192(4):523-5.
10. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med. 2015;3(6):435-42.
11. Cooper CB, Barjaktarevic I. A new algorithm for the management of COPD. Lancet Respir Med. 2015;3(4):266-8.