

coronavirus disease (COVID-19) pneumonia. The real concern is that, at the time of our writing, the pandemic has caused about 1 million deaths initiated by pneumonia and respiratory failure. Because intensive care mortality has been reported to range from 10–20% to 80–90% of patients needing respiratory assistance, it is appropriate to ask ourselves to what extent different treatment choices may have contributed to such high differences in mortality. Indeed, it is conceivable that ill-timed decisions or inappropriate ventilatory settings may worsen the natural course of the disease. In this framework, the well-documented observations of heightened drive and sudden deterioration in patients with COVID-19 imply the genuine possibility of patient self-inflicted lung injury (P-SILI). It is also to be remembered that there exists a body of literature produced by other experts that expresses similar concerns and documents the reproducible nature of P-SILI (3–9). No one is entitled to pontificate on issues to which neither we nor Tobin and colleagues have found the answers. (We certainly are not “claiming” to know specifics, contrary to what the repeated mantra “Gattinoni and colleagues claim...” suggests.) However, in the context of the pressing clinical need to formulate a logical approach, an informed editorial hypothesis should be welcomed. Our intent was to underline that the assessment of abnormal drive is a step forward toward better understanding (and treatment) of COVID-19 pneumonia. Indeed, although the interplay between respiratory drive, muscular work, and applied energy is complex and far from completely understood, the possibility of excessive self-induced stress, strain, and edema (P-SILI) in these inflamed lungs must be taken into account. The work from Esnault and colleagues calls attention to this potential problem and is a first step toward its better understanding. Every measurement has its own biases and limitations, but measuring the strength of the respiratory drive and monitoring its changes must be better than not doing so and basing key decisions regarding respiratory support on mere guesswork. ■

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## The Role of Eosinophils during the Withdrawal of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease



To the Editor:

We read with great interest a *post hoc* analysis of the IMPACT trial that investigated the effect of inhaled corticosteroid (ICS) withdrawal in patients with chronic obstructive pulmonary disease (1). Han and colleagues (1) demonstrated that the benefit of fluticasone furoate/umeclidinium/vilanterol combination therapy on exacerbation reduction, lung function, and quality of life was not associated with the abrupt withdrawal of ICSs in the IMPACT trial (1, 2). However, we wonder whether the baseline eosinophil count would play another important role that could impact the effect of ICS withdrawal.

In the European Respiratory Society guideline (3), which is based on the analysis of four studies, COSMIC (4), WISDOM (5), INSTEAD (6), and SUNSET (7), they strongly recommend that ICSs should be continued in patients who have blood eosinophil counts  $\geq 300$  cells/ $\mu\text{l}$ , with or without a history of frequent exacerbations. In this meta-analysis (3), they found that no effect of ICS withdrawal was observed on exacerbation rate (rate ratio [RR], 1.03; 95% confidence interval [95% CI], 0.90–1.18;  $P = 0.71$ ;

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$I^2 = 0\%$ ) in patients with eosinophil counts  $<300$  cells/ $\mu\text{l}$ ; however, a significant increase in the rate of exacerbations was found in the subgroup with eosinophil counts  $\geq 300$  cells/ $\mu\text{l}$  (RR, 1.63; 95% CI, 1.24–2.14;  $P = 0.0005$ ;  $I^2 = 0\%$ ). In fact, the Global Initiative for Chronic Obstructive Lung Disease guideline also suggested the use of ICSs in patients with eosinophil counts  $\geq 300$  cells/ $\mu\text{l}$  or eosinophil counts  $\geq 100$  cells/ $\mu\text{l}$  and  $\geq 2$  moderate exacerbations/1 hospitalization (8). All these recommendations (3, 8) indicate the importance of eosinophil count when clinicians consider the withdrawal of ICSs.

In this correspondence, we raised concerns regarding baseline eosinophil count among prior ICS users in this *post hoc* analysis and whether the baseline eosinophil count level would impact the effect of ICS withdrawal. Especially for patients with eosinophil counts  $\geq 300$  cells/ $\mu\text{l}$ , the abrupt withdrawal of ICSs in this specific population is expected to have a greater negative impact than that in other groups. Therefore, further subgroup analysis in this study (1) according to baseline eosinophil count among prior ICS users is needed to clarify this issue. ■

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## Reply to Wang and Lai



From the Authors:

Thank you for the opportunity to respond to the letter to the editor written by Dr. Cheng-Yi Wang and Dr. Chih-Cheng Lai on our article, “The Effect of ICS Withdrawal and Baseline Inhaled Treatment on Exacerbations in the IMPACT Study: A Randomized, Double-Blind Multicenter Trial” (1). We thank Dr. Wang and Dr. Lai for the opportunity to provide additional data on the relationship between baseline eosinophil level and inhaled corticosteroid (ICS) withdrawal in IMPACT (Informing the Pathway of Chronic Obstructive Pulmonary Disease Treatment).

The primary question asked is whether baseline eosinophils impact the effects of ICS withdrawal. To be clear, the intent of IMPACT was not to study ICS withdrawal. Only roughly 14% of the patients in the trial were withdrawn from ICSs. In Figure 1, we show the exacerbation rate for all three treatment arms versus baseline eosinophil count, stratified by ICS use at entry to the study.

To answer Dr. Wang and Dr. Lai’s question on ICS withdrawal, we must compare the fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) treatment arm with the UMEC/VI treatment arm among those previously on ICS. In Figure 2, we show the exacerbation rate ratio for FF/UMEC/VI compared with UMEC/VI plotted against baseline eosinophil count. Based on the point estimates alone, we see a numerical reduction in exacerbation rates for FF/UMEC/VI versus UMEC/VI across all eosinophil levels in the prior-ICS group. For Figure 2, the upper bound of the confidence limit for FF/UMEC/VI compared with UMEC/VI falls below unity at approximately 50 eosinophils/ $\mu\text{l}$ . There is also a numerical reduction in exacerbation rates for FF/UMEC/VI compared with UMEC/VI for those with eosinophil levels greater than 150 eosinophils/ $\mu\text{l}$  in the no-prior-ICS group. It should be noted that the confidence intervals for the individual treatment arms (Figure 1) and the treatment differences (Figure 2) are much wider for the non-ICS group owing to the much smaller sample size and lower event rate in this subgroup.

Overall, in those previously on ICSs, we see a numerical reduction in exacerbations for FF/UMEC/VI compared with UMEC/VI irrespective of baseline eosinophil levels with greater effect among those with higher eosinophil counts. As mean eosinophil

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