

The authors reply: We agree with Drs. Rolla and Brussino on the importance of vaccination for patients with COPD. In the IMPACT trial(1) we advocated best care and recommended that all patients be offered influenza and/or pneumococcal vaccine if they were not up-to-date.

Unfortunately, overall global vaccination rates were low, with only 17% overall reporting vaccinations. Incidence of vaccinations were similar across the study arms (17% ICS/LAMA/LABA, 16% ICS/LABA, 16% LAMA/LABA). The authors believe further efforts should be made to help improve overall vaccination rates in clinical care.

The authors disagree with Dr. Wedzicha and colleagues and believe differences in study design and patient populations clearly explain the differences between FLAME(2) and IMPACT. They also promulgate a circular argument, because if they believe ICS withdrawal is harmful, they must also believe that ICS therapy is beneficial for appropriate ~~some~~ patients who carry a diagnosis of COPD. The studies evaluated different patient populations, with ~30% in FLAME and ~70% in IMPACT being GOLD D by current classification(3). IMPACT was designed to study a typical COPD population, generalizable to clinical practice. By excluding a current diagnosis of asthma and using the same criteria as previous studies, but allowing inclusion of a past history of asthma,(4) the IMPACT population is easily recognized by practicing physicians. All patients met ATS/ERS criteria(5) for COPD; had a mean age of 65 years, demonstrated fixed airflow obstruction with mean FEV<sub>1</sub>=45.5%, and a heavy smoking history of ~47 pack-years. IMPACT investigators excluded patients whose symptoms were not due to COPD. In contrast, the FLAME study should be interpreted with caution as it enrolled a population enriched for patients unlikely to benefit from inhaled corticosteroids (ICS), since investigators would not enroll subjects who require ICS in a 4-week run-in with tiotropium monotherapy. This effectively biased the trial against finding a benefit for ICS. FLAME also excluded patients with blood eosinophil levels >600 cells/μL. The FLAME and IMPACT trials addressed different patient populations; clinicians should consider these differences in decision making.

Dr. Petite questions if ICS withdrawal contributed to the efficacy observed with triple therapy compared to dual therapy. IMPACT was not a steroid withdrawal trial. Approximately 70% entered the trial on an ICS-containing regimen, yet only 20% were randomized to LAMA/LABA. Therefore, only 14% of the IMPACT trial participants had ICS withdrawal. This did not contribute significantly to the observed study effects and we continued to see exacerbations throughout the study, not only in the first month where the ICS withdrawal effect would be greatest.

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Since publication of their article, the authors report no further potential conflict of interest.

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