Blood eosinophilis as a continuous variable in the treatment of COPD
van den Berge, Maarten; Kerstjens, Huib Am

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The efficacy of inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD) has been the subject of much debate. Additionally, their use has been associated with adverse events such as pneumonia. Therefore, identification of patients with COPD who are most likely to benefit from ICS, with reduced likelihood of adverse events, is important, even more so with the advent of triple therapy.

The IMPACT study\(^1\) was the largest study, to date, to investigate the efficacy of triple therapy versus ICS–LABA and versus LABA–LAMA in patients with moderate-to-severe COPD at risk of exacerbations. Triple therapy reduced the exacerbation rates and improved lung function and quality of life compared with either dual combination. In addition, ICS–LABA reduced exacerbation rates more than LABA–LAMA\(^1\). In a simple binary analysis, the reduction in incidence of exacerbations was greater with higher blood eosinophil counts. In *The Lancet Respiratory Medicine*, Steven Pascoe and colleagues\(^2\) use the large sample size of IMPACT (n=10355) for detailed analyses of the value of blood eosinophils as a biomarker, modelled in a continuous way rather than using arbitrary cutoffs. They found a greater reduction in exacerbations at eosinophil counts higher than 100 cells per μL with triple versus LABA–LAMA, and with ICS–LABA versus LABA–LAMA. The risk of pneumonia was not associated with baseline blood eosinophil counts. These results certainly provide some support for the new recommendations in the GOLD 2019 report,\(^3\) which compared triple therapy and ICS–LABA with LABA–LAMA in patients with COPD, irrespective of exacerbation history, and also showed that the effects of ICS are dependent on a continuum of eosinophil counts. These findings may have important consequences because they suggest that adding ICS to LABA alone or to LABA–LAMA might additionally be considered in patients with eosinophilic COPD (eg, >300 eosinophils per μL) who are symptomatic but do not have exacerbations. It is important to note that 7351 (71%) of 10355 patients included in IMPACT already used ICS at baseline, which could have been a confounder. It would be of interest to perform additional sub-analyses to assess treatment effects in patients who did not use ICS, LABA, or LAMA at the start of the study.

Until recently, most clinicians did not associate eosinophilia with COPD, although it was recognised that there was an association between increase in eosinophil count and impending exacerbations.\(^6\) Analyses have clearly shown increased eosinophil counts in blood and sputum,\(^7\) but their pathobiology is rather unclear. Indeed, it is likely that several different causes could lead to increased eosinophil counts and might yet associate differently with corticosteroid responsiveness. This association with the pathobiology of increased eosinophil counts and steroid responsiveness should

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**Blood eosinophils as a continuous variable in the treatment of COPD: impact on the guidelines**

The efficacy of inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD) has been the subject of much debate. Additionally, their use has been associated with adverse events such as pneumonia. Therefore, identification of patients with COPD who are most likely to benefit from ICS, with reduced likelihood of adverse events, is important, even more so with the advent of triple therapy.

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be studied in more detail, as should the relevance of higher eosinophil numbers in stable COPD versus during exacerbations and the stability of the measurements of blood eosinophil counts.

The results of the IMPACT and KRONOS studies provide important new insights in the role of blood eosinophils as a continuous parameter to predict ICS treatment response in COPD. Increasing numbers of treatable traits and more detailed use of eosinophil counts (as a continuous variable) render personalised medicine increasingly feasible. Unfortunately, increasing numbers of traits and counts do render use of these data more complex for the practicing clinician. Web-based algorithms will be needed to define and make optimal treatment guidance applicable for personalised patient advice and shared decisions. Such algorithms, however promising, should be tested prospectively.

*Maarten van den Berge, Huib AM Kerstjens
Department of Pulmonary Diseases, University Medical Center Groningen, and Groningen Research Institute for Asthma and COPD, University of Groningen, NL–9700-RB Groningen, Netherlands
m.van.den.berge@umcg.nl

Prospects and challenges of a new live tuberculosis vaccine

An effective vaccine against tuberculosis is urgently needed. In this issue, Michele Tameris and colleagues report the results of a randomised, double-blind, dose-escalation trial of a new tuberculosis vaccine, MTBVAC, compared with BCG in a small group of adults and infants in South Africa. By contrast with most other novel tuberculosis vaccines, MTBVAC is a live vaccine based on an attenuated strain of *Mycobacterium tuberculosis*. With around 4000 genes and a broad functional armamentarium, ranging from dormancy and intracellular survival to immune escape, *M tuberculosis* has successfully infected humans for thousands of years. Thus, it is not surprising that around 25% of the world’s population is infected with this pathogen, which is transmitted via respiratory droplets. Although tuberculosis is now the deadliest infectious disease caused by a single pathogen, more than 90% of ostensibly immunocompetent individuals with *M tuberculosis* can successfully contain their infection, remain asymptomatic, and never develop the disease. Experimental results in non-human primates and epidemiological data from humans provide evidence that previous *M tuberculosis* infection protects against new infection. By analogy, one would hope that MTBVAC, in which two crucial *M tuberculosis* virulence genes (phoP and fadD26) have been deleted, could induce an immune state similar to latent tuberculosis infection and reduce the risk of subsequent active infection and disease.

The available BCG vaccine, which is based on an attenuated *Mycobacterium bovis* strain, was developed at the beginning of the 20th century. Several regions of difference, comprising hundreds of virulence genes, were deleted in BCG. These deletions afforded remarkable safety but could have compromised immunogenicity and protective efficacy. Even though BCG vaccination can lead to modest (around 19%) prevention of *M tuberculosis* infection and protects against the development of disseminated disease in early childhood, around 1 million children develop intrathoracic tuberculosis yearly in regions where the vaccine is administered. Furthermore, the BCG vaccine has variable and