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Effects of Anti-IL-5 on Virus-induced Exacerbation in Asthma Light and Shadow

Viral infections are among the most frequent causes of asthma exacerbation (1). The prevention and/or treatment of viral-induced asthma exacerbations are still unmet medical needs. Indeed, these events, characterized by a transient impaired responsiveness to corticosteroids (2), occur despite appropriate asthma treatment (3). The identification of novel pharmacological approaches able to affect viral-induced asthma exacerbations has the potential to affect the natural history of the disease.

Treatment with anti-IL-5 is a very effective pharmacological intervention to quench eosinophilic inflammation, with current clinical indications in severe eosinophilic asthma and in eosinophilic granulomatosis with polyangiitis (4, 5).

Eosinophils are also important for innate and adaptive immune responses to pathogens (6, 7). Investigating the effects of mepolizumab on virus-induced immune response and on viral infection outcomes is of major clinical relevance.

In this issue of the *Journal*, Sabogal Piñeros and colleagues (pp. 508–517) report the results of an interesting study in which mild steroid-naïve patients with asthma were randomly assigned to receive (irrespective of the blood eosinophil levels) either 750 mg intravenous mepolizumab or placebo in a double-blind manner (8). Two weeks after the injection, the patients were experimentally infected with rhinovirus 16. The study shows that mepolizumab treatment reduced eosinophil activation but did not prevent activation of the remaining eosinophils in response to a rhinovirus 16 challenge. The lack of effect of anti-IL-5 in mild asthma may relate to the remaining activated eosinophils and the altered humoral and cellular immune response to a viral challenge.

The study has the merit to investigate immunological pathways related to triggers that are relevant in real life, and to provide some previously unexplored *in vivo* effects of mepolizumab on immune response to rhinovirus. Mepolizumab induced the potentiation/activation of key elements of the immune response to viral infection (9, 10), including enhanced systemic NK cells, prevention of rhinovirus 16 depletion of B-lymphocytes in BAL fluid, and enhanced secretory IgA. However, patients receiving mepolizumab showed significant higher viral load in nasal swabs, reflecting either enhanced viral replication rates or reduced viral clearance. These data suggest that, despite the fact that mepolizumab treatment promotes pathways with antiviral/antimicrobial activities, the overall changes in the immunologic response yield to pro-infective results. Possibly, the

anti-IL-5-induced reduction of eosinophils [with their innate immune activities (11)] and the attenuation of neutrophil response to the viral challenge (involved in the inflammatory response to viral infection) have a role in these outcomes.

Interestingly, previous studies have shown a negative interplay between the T2 inflammatory milieu (including eosinophils) and the efficacy of the immune response to infections (12). *In vitro* inhibition of T2 inflammatory mediators resulted in enhanced antiviral/antimicrobial activity (12). *In vivo*, treatment with humanized monoclonal anti-IgE antibodies (omalizumab) in children with mild asthma resulted in a significant reduction of viral-induced exacerbation of asthma (13, 14). This positive clinical effect was paralleled by blood leukocytes-enhanced innate immune response to viral infection and, at variance with the finding reported in study by Sabogal Piñeros and colleagues, decreased viral shedding in nasal mucus samples (8, 13). These data suggest that targeting IgE versus eosinophil may result in different clinical outcomes of the viral infection in asthma.

Modulation of T2 inflammatory mediators (including IL-5, IL-13, and IgE) is the novel forefront of asthma treatment. Further studies are needed to better understand the specific mechanisms of action of the biological treatments targeting different biomarkers. In particular, whether these pharmacological approaches can fill the gap in the prevention and treatment of viral-induced asthma exacerbation must be tested in specifically designed studies.

Inevitably, every light has its shadow. The study by Sabogal Piñeros and colleagues does not inform on the clinical effect of mepolizumab in this setting. Indeed, the study was powered for a primary lung function outcome, and no clinical effect was expected. Mepolizumab did not affect lung function or asthma control scores both at baseline and after the experimental infection. The variability of the markers assessed in the study, with significant changes in sputum eosinophils (their Figure 3) and in blood eosinophil activation (see Table E1 in their online supplement) in the placebo group before any intervention, and the very weak eosinophilic response [at variance with previous studies (15)] after rhinovirus 16 challenge, question the design of the study and should prompt stringent control conditions in future studies.

Certainly, proof-of-concept studies similar to the one published in this issue of the *Journal* by Sabogal Piñeros and colleagues are of inestimable value and must not be ignored by the scientific community (8). Indeed, by providing light and shadow, they can stimulate the development of new working hypothesis, and thus favor our understanding of the mechanisms of the disease and promote the progress of asthma management. ■

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Clinical Significance of Viral Detection in Critically Ill Patients More Questions Than Answers

In spite of advances in antibiotic drug development, the successive recommendations on antibiotic therapy, and all the technical improvements in intensive care support, pneumonia remains a leading cause of death in the world (1). The mortality rate varies according to the severity of disease, ranging from less than 5% in outpatients to more than 30% when patients need to be admitted to the ICU (2). In addition, recent data showed that, even in patients with pneumonia who have been appropriately treated, the 30-day mortality rate is still above 10% (3). This suggests that there is room for research and improvement assessing the role of additional interventions or adjuvant therapy.

Despite routine microbiological testing in severe pneumonia, microbial diagnosis is obtained only in half of patients admitted to the hospital, with bacterial agents the most commonly identified microorganisms (4). However, the emergence of severe acute respiratory syndrome, avian influenza A virus, Middle East respiratory syndrome coronavirus, and the 2009 pandemic influenza pointed out the important role of respiratory viruses, *per se*, as causes of severe pneumonia.

In immunocompromised patients, pneumonia is a main cause of morbidity and mortality. Immunodeficient patients have several risk factors that contribute to an increased risk for development of respiratory tract infection. Lung infections in immunocompromised patients can be caused by a much broader number of pathogens that include Gram-negative bacilli and *Staphylococcus aureus*, fungus such as *Aspergillus fumigatus*, or viruses. In hematopoietic stem-cell transplant recipients' respiratory syncytial virus (RSV), human metapneumovirus, cytomegalovirus, parainfluenza viruses, and influenza viruses are well known for their potential to cause fatal pneumonia.

In this issue of the *Journal*, Legoff and colleagues (pp. 518–528) (5) performed a *post hoc* analysis of a prospective multicenter cohort study of critically ill hematology patients (6) to assess the clinical effect of a positive virus polymerase chain reaction test in nasopharyngeal swabs at ICU admission. The nasal swabs were performed in 747 patients (447 with acute respiratory failure [ARF]), in whom 21.3% tested positive (56.4% rhinovirus/enterovirus and 30.7% influenza/parainfluenza/RSV).

A first observation is that although respiratory viruses were more frequently detected in patients with ARF (25.3%), 16.3% of those without ARF tested positive, as well as 14.1% without any respiratory symptom. In addition, viral distribution was