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Biological Treatments for Eosinophilic Asthma Enter the Airways

There are several new available biological treatments such as the anti-IL-5 monoclonal antibodies (mAbs) mepolizumab and reslizumab and the IL-5 α (IL-5 receptor α) blocker, benralizumab, for the treatment of severe eosinophilic asthma (1, 2). Dupilumab, which targets IL-4 α blocking the IL-4/IL-13 signaling pathways, is moving through the approvals process (3). Lebrikizumab and tralokinumab are anti-IL-13 mAbs that improved lung function in patients with poorly controlled asthma, yet the development of these drugs was ultimately halted because of a lack of clinical efficacy in phase 3 clinical trials (4, 5). IL-13 is produced in the airways after exposure to allergens and is involved in mucous hypersecretion, bronchial hyperresponsiveness, epithelial metaplasia, and airway remodeling (6, 7). Given its pivotal role in many of the key pathophysiological processes in acute and chronic allergic inflammation, it is somewhat surprising that mAbs targeting IL-13 were not more clinically effective in patients with this asthma phenotype. One potential explanation is that these mAbs do not achieve sufficient concentrations to effectively target receptors in the bronchial airway epithelium, mast cells, and mononuclear cells in the lung (8); in fact, mAb transport from the serum to the lung is poor in all species, with serum levels of mAbs 500–10,000 times higher than those in BAL after intravenous administration (9, 10). Therefore, to determine whether direct airway delivery is an effective and safe alternative to systemic administration, in this issue of the *Journal*, Lightwood and colleagues (pp. 610–619) evaluated the effectiveness of CDP7766 in a model of allergic asthma in cynomolgus macaques naturally sensitized to *Ascaris suum*. CDP7766 is an inhaled mAb Fab fragment that acts by blocking IL-13 binding to IL-13 α 1 and IL-13 α 2 (11). This was administered via an eFlow nebulizer, producing particles with median aerodynamic diameter of 3.2 μ m (SD, 1.5), which fall within the respirable fraction capable of reaching the terminal bronchioles. The target dose was delivered over the course of 6 minutes, using a breath simulation algorithm. The experiment consisted of allocating 32 macaques to five

daily consecutive treatments with vehicle or varying CDP7766 concentrations (60, 10, or 1 mg/d). Sensitization was performed via 15 breaths of ultrasonic nebulized *A. suum* at screening 4–6 weeks before any treatment, and during Days 3 and 4 of the CDP7766 treatment protocol. BAL was collected 24 hours after the last sensitization dose.

Sensitization increased airway resistance, eosinophil numbers, and cytokine levels, particularly IL-5, which had marked more than 10-fold elevation. Treatment with CDP7766, regardless of dose, did not significantly reduce airway eosinophilia when compared with vehicle. However, relative to the eosinophilia induced during the screening 4–6 weeks before treatment, the 60 mg/day dose significantly reduced the degree of sensitization-induced airway eosinophilia. CDP7766 markedly lowered the levels of all cytokines measured in the BAL, with the exception of eotaxin-1, TARC (thymus- and activation-regulated chemokine), IP-10 (IFN- γ -induced protein 10), MCP-1 (monocyte chemoattractant protein 1), and IL-4, IL-2, and IL-1 β . It also blunted the increase in airway resistance measured on Day 2.

Overall, there are many reasons why to feel excited about the possibilities that can potentially arise from the results of this study. Although performed in nonhuman primates, it clearly demonstrates that nebulized IL-13 mAbs Fab fragments can effectively lower airway eosinophilia by $\sim$ 30%, while reducing T2-related cytokines by $\sim$ 78% and preventing increased airway resistance. Blocking the effect of IL-13 directly in airway epithelium could potentially result in stronger MUC5AB inhibition (6), leading to better mucous secretion control, and long-term use could reduce epithelial remodeling and subepithelial fibrosis. Also, it could have stronger effects on airway smooth cells, and thus explain why CDP7766 was able to reduce airway resistance, whereas previous clinical studies of anti-IL13 mAbs in patients with mild asthma failed to prevent allergen-induced bronchial hyperresponsiveness (12). The use of Fab fragments instead of full-length mAbs is an exciting proposition, as these are smaller, could have better lung deposition, are potentially less immunogenic, and have a high affinity and specificity for IL-13 (10, 12). Further, using a vibrating membrane nebulizer ensures that the particles generated are mostly in the respirable fraction, ensuring more distal airway deposition (12). In addition, given that Fab

fragments have low systemic bioavailability when delivered into the airways, this limits the potential for systemic toxicity (10). For example, CDP7766 did not affect peripheral blood cell counts, whereas clinical studies have shown that anti-IL-3 mAbs can be associated with increased peripheral blood eosinophilia (4).

There are significant limitations to the study and many questions that still need to be answered. The study was of very short duration, and thus it is not known whether CDP7766 would be effective for longer periods, including whether it could potentially reduce exacerbations. In addition, mAbs Fab fragments were delivered using a tidal breathing algorithm in the absence of any underlying airway disease; however, in patients with severe asthma, underlying changes in ventilation parameters and airway function and structure could significantly affect the physical properties of the aerosol (size, density, and shape) particles and their deposition rate, potentially affecting its clinical effectiveness (10). Regardless of these limitations and uncertainties, the data presented in this study strongly support the development of phase 1 clinical studies in patients with severe eosinophilic asthma and the potential to deliver biological therapies directly into the target organ while reducing the potential for adverse systemic effects. ■

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Telehealth for Chronic Obstructive Pulmonary Disease: Promises, Populations, and Personalized Care

The paper by Walker and colleagues (pp. 620–628) in this issue of the *Journal* reports (yet another) negative trial of telehealth for chronic obstructive pulmonary disease (COPD) (1). Globally, the burden on healthcare services and impact on the quality of life of individuals with COPD is huge and increasing. Despite much rhetoric about the potential of telehealth to reduce this burden, trials have generally been disappointing, consistently showing no effect on admissions or quality of life, and typically increasing rather than reducing healthcare demand (2–4). This is particularly disappointing given the growing evidence of benefit in other long-term conditions such as hypertension (5), diabetes (6), and heart failure (7). What is going wrong?

In hypertension and diabetes, the aim is to control an asymptomatic condition in which providing patients with the means to measure their blood pressure or blood sugar, linked (crucially) with a mechanism for professional support, influences the patients' perception of their condition and engages them in their self-management (8). In symptomatic, exacerbating conditions, the primary aim is to promote timely treatment of attacks and thereby reduce admissions. This is predicated on the assumption that exacerbations can be detected early in their course, and that timely treatment prevents further deterioration (9). In heart failure, imminent deterioration can be detected by monitoring weight (10). In COPD, no such clear predictor has emerged. Patients struggle to distinguish "normal" fluctuations in their symptoms from imminent exacerbations (11), symptom scores are little better than chance (12), small changes in oxygen saturation

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