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Commentary

Revisiting IL-13 blockade: can we reach the wonderland the inhaled way?

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Interleukin-13 (IL-13) is expressed by airway structural cells in patients with asthma and has an active role in airway hyperresponsiveness, inflammation, mucous metaplasia and airway remodeling [1] while it seems to be an important biomarker in severe asthma [2]. Thus, blockade of IL-13 should plausibly alter airway inflammation and hyperresponsiveness, making this cytokine a possible target for the development of novel therapies. Recent studies using anti-IL-13 antibodies, lebrikizumab [3] and tralokinumab [4], failed to provide consistent improvement in patients with severe T2 high asthma, despite some initial promising results in patients with evidence of T2 high inflammation, as expressed by increased serum periostin [5]. Since the promising Phase II results for lebrikizumab [5] and tralokinumab [4] were not confirmed in Phase III trials, a better understanding of the responder population for anti-IL-13 blockade is necessary. In this issue, the study of Burgess et al. [6] provide data of the administration of a humanized, high-affinity, neutralizing, anti-human-IL-13 antibody fragment, administered through the inhaled route, giving an alternative to the systemic administration of monoclonal antibodies for the therapy of asthma and mimicking the usual practice of drug delivery in asthmatic patients. This study has a proof-of-concept element, as the observed FeNO suppression shows an anti-inflammatory effect of this agent, while the numerical increase of FEV_1 (with a mean difference of 150–200 mL versus placebo) shows an important treatment efficacy, both these improvements need to be confirmed in later phase trials. The difference in efficacy of this inhaled anti IL-13 antibody compared to injectable anti-IL-13 medicines is something that needs to be considered, as this potential option moves along its development pathway. The fact that in the study of Burgess et al. [6] there is a lack of a dose-response relationship for both FeNO and FEV_1 is a potential issue that needs to be considered in future trials of this agent.

Approximately 10% of asthmatic patients are suffering from severe asthma that requires treatment with high doses of inhaled corticosteroids and bronchodilators in order to achieve disease control, or remain uncontrolled despite this treatment [7]. Historically, patients with severe uncontrolled asthma were mainly treated with oral corticosteroids which are known to be associated with severe adverse events. Therefore, in the latest years there is an effort to replace oral corticosteroid therapy with biological agents, mainly monoclonal antibodies, targeting specific inflammatory pathways. Some of these agents have been already been licensed and are suggested as first line therapy for severe uncontrolled asthma [8].

The inhaled route of administration of a monoclonal antibody is an attractive non-invasive approach which offers the potential to deliver the drug directly to the target organ (i.e the airways and lung tissue). Thus, it seems to have advantages compared to the systemic (either intravenous or subcutaneous administration) as it is related to an early onset of action and provides greater treatment efficacy at lower doses with less systemic exposure and probably fewer adverse events. However, the biggest challenge of any novel anti-inflammatory treatment for asthma, especially if provided via the inhaled route, is that it needs to be compared with the standard of care which includes inexpensive very efficient anti-inflammatory medicines like inhaled corticosteroids (ICS), and all the issues that need to be addressed such as the inhaler technique, critical errors during the use of the device and patients' adherence to inhaled medication.

When evaluating a novel medicine, we should always apply the fundamental principle of Hippocrates “first do not harm”. The study of Burgess et al. [6] shows that inhaled anti IL-13 seems to be safe both in healthy participants and in mild asthmatics. However, following drug inhalation, a significant percentage of these mild asthmatic patients developed bronchospasm and FEV_1 reduction which in some cases was significant and potentially clinically relevant. This observation suggests that the safety of this agent needs to be very carefully considered in patients with more severe asthma and probably greater lung function impairment.

Overall, this study shows that the inhaled route can be an alternative choice to reach the expected efficacy of IL-13 suppression in patients with asthma. The results are promising, but still it is necessary to test the efficacy and safety of this agent in a population of patients with more severe asthma and to compare it with the current standard of care. Only time will tell if these promising results will lead to the development of more potent inhaled biologics.

Disclosure

“The authors declare no conflicts of interest”.

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