Tezepelumab: A new pathway to asthma control

Our understanding of the complex mechanisms of inflammation, which result in the clinical entity we call 'asthma', has improved exponentially over the last few decades. This knowledge has resulted in the development of targeted biological therapy with several monoclonal antibodies, including those directed against IgE (omalizumab), interleukin-13 (tralokinumab), interleukin-5 (mepolizumab and reslizumab), and the alpha subunits of the interleukin-4 and interleukin-5 receptors (dupilumab and benralizumab).[1] One might be tempted to think that tezepelumab is simply another agent in this group; however, it is distinct from its predecessors in a way that may result in it having a far broader application. It is an investigational humanised IgG2 monoclonal antibody that blocks the action of thymic stromal lymphopoietin (TSLP) on its receptor complex, and exerts its effects on the inflammatory cascade far upstream of the agents mentioned previously. TSLP is an epithelial cell-derived cytokine produced in response to environmental and proinflammatory stimuli including tobacco, diesel smoke and viruses. It is central to the regulation of type 2 inflammation through its activity on dendritic cells, T and B cells, as well as mast cells, basophils, natural killer T cells, innate lymphoid cells, and even neutrophils.[2]

Corren *et al*.[2] examined the efficacy and safety of tezepelumab in uncontrolled asthmatics, in a recent industry-sponsored, phase 2, randomised, double-blind, placebo-controlled trial (PATHWAY). The group reported encouraging results: 3 dose levels of tezepelumab were compared with a placebo and resulted in a reduction in the annualised exacerbation rate by 61%, 71%, and 66% at week 52, respectively. Importantly, these differences were independent of baseline blood eosinophil counts and other Th2 biomarkers, though there was a substantial and persistent decrease in blood eosinophil count and fractional expired nitric oxide levels observed in the treatment groups. In all tezepelumab groups, the pre-bronchodilator forced expiratory volume in 1 second at week 52 was >100 mL higher than in the placebo group. Though there was one fatal serious adverse event in the treatment group, the overall rate of adverse events did not differ in comparison with the rate observed in the placebo group.

These results highlight the potential advantages of targeting an upstream cytokine such as TSLP, which suggests that the future of asthma biologics may be in agents that affect disease activity more broadly than inhibition of a single downstream pathway.

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