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Tezepelumab: A Novel Modality of Treatment in Refractory Asthma?

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Asthma is a chronic disease characterized by inflammation and obstruction of the airways, whose cornerstone of treatment is inhaled or systemic glucocorticoids. However, corticoids may not be enough to manage refractory disease, thus severely increasing disease burden, impairing quality of life and exposing patients to the adverse effects of increasing doses of systemic corticoids [1]. Consequently, many molecular targets constitute the basis for steroid-sparing biologic therapies (such as IgE and type 2 helper T (Th2) cytokines, like IL-4, IL-5, IL-13, and their respective receptors) that may benefit patients with uncontrolled asthma alongside inhaled glucocorticoids and long-acting beta-agonist (LABA) therapy.

Tezepelumab is a human IgG2 monoclonal antibody that binds to the thymic stromal lymphopoietin (TSLP), thus down-regulating production of cytokines by antigen-specific Th2 cells and decreasing airway inflammation. Although clinical trials are still in early stages, Tezepelumab has shown promising results as a potential treatment that may revolutionize asthma treatment and alter the course of refractory disease [1].

Several clinical trials (phase 2b PATHWAY, 2017, phase 3 NAVIGATOR, 2021) concluded that Tezepelumab was effective in reducing the annualized asthma exacerbation rate (AAER) compared with placebo in patients with severe, uncontrolled asthma, as well as decreasing inflammatory markers (FeNO, IgE, eosinophil count), and improving lung function, asthma control, and patient health-related quality of life in the overall population [1,2]. Further exploratory analyses of the NAVIGATOR study found that Tezepelumab comparably reduced annualized asthma exacerbation rates (AAER) in both Omalizumab-eligible and Omalizumab-ineligible patients [3]. This reduction in AAER was also found to be irrespective of number of perennial aeroallergen sensitivities, of baseline asthma bronchodilator reversibility, and of BMI [4-6]. All of which suggests that Tezepelumab improves outcomes in poorly controlled asthma across a wide range of patients. Moreover, reported adverse effects were similar in both Tezepelumab and placebo groups (nasopharyngitis, asthma, and upper airway infection), which makes it a relatively safe treatment [7].

Tezepelumab was also proved to decrease inflammatory markers in the airway mucosa, which correlates to better outcomes in treatment. CASCADE is another double-blind, randomized, placebo-controlled, phase 2 trial, aimed at studying change in airway submucosal inflammatory cells in bronchoscopy-biopsy samples in a 28-weeks follow-up [8]. Results revealed reduced airway eosinophil counts in the Tezepelumab arm, regardless of baseline blood eosinophil count, alongside reduced airway hyperresponsiveness, and reduced serum inflammatory biomarkers (blood eosinophils, FeNO, serum IL-5 and IL-13, and plasma eosinophil-derived neurotoxin). However, no change from baseline in spirometry (FEV1) or in frequency in exacerbations was observed. Additionally, inhibiting TSLP-signaling by Tezepelumab was associated with a reduction of airway hyperresponsiveness (mainly to Mannitol) and a decrease in eosinophil counts in both tissue and broncho-alveolar lavage, consequently reducing airway inflammation [9].

To summarize, there is undoubtedly a need for alternative, corticoid-sparing therapies in refractory asthma. Hence, Tezepelumab may be an option that could revolutionize asthma treatment. Early results that prove its efficacy in reducing hospitalizations, hospitalizations' duration, intensive-care unit stay, and emergency-department visits due to asthma exacerbations are very encouraging [10]. Tezepelumab's corticoid-sparing effect is yet to be confirmed as evidence is inconclusive [7]. Nonetheless, more clinical trials and more evidence may be needed to solidify Tezepelumab's role and cost-effectiveness in controlling severe disease.

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