Tezepelumab in the Treatment of Severe Asthma

An Expert Interview with Andrew Menzies-Gow

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Asthma affects around 339 million people worldwide,[1] with approximately 10% of these experiencing severe disease.[2] Despite many advances in asthma therapy in recent years, including the advent of biologic therapies, many patients with severe asthma cannot control their symptoms.[2,3] Severe, uncontrolled asthma is extremely debilitating and involves frequent exacerbations, significant limitations on lung function and a reduced quality of life.[2,3] Patients are also at risk of increased mortality and hospitalization,[4] and severe, uncontrolled asthma remains a significant health and economic burden.[5]

In December 2021, tezepelumab (Tezspire®, AstraZeneca and Amgen, Cambridge, UK and CA, USA) was approved following a Priority Review by the United States Food and Drug Administration (FDA). Approval was based on results from the PATHFINDER clinical trial programme, including the NAVIGATOR Phase III trial (ClinicalTrials.gov Identifier: NCT03347279) in which tezepelumab showed superiority compared with placebo across every primary and key secondary endpoint in patients with severe asthma, when added to standard therapy.[6] In an expert interview, Professor Menzies-Gow discusses tezepelumab and its likely impact on clinical practice.

Q: What is the mechanism of action of tezepelumab?

Tezepelumab is a human monoclonal antibody that blocks the activity of thymic stromal lymphopoietin (TSLP), a key epithelial derived cytokine, which sits at the top of the inflammatory cascade. When we breathe in things that can affect our lungs such as allergens, pollution, viruses, and cigarette smoke, they can increase the release of epithelial derived cytokines such as TSLP and also IL-25 and IL-33. We know that TSLP can drive classic allergic inflammation via the T helper (TH2) cells and B cells, which produce too much immunoglobulin E, leading to an allergic response. It can also impact on the innate immune response via the innate lymphoid cells type 2, which produce large amounts of IL-5 and IL-13 and drive eosinophilic asthma. From clinical studies to date, we also know that TLSP has an impact on airway hyperactivity. Therefore, Tezepelumab inhibits a very broad acting upstream cytokine.

Q: Could you give us a brief overview of the clinical data leading to the FDA approval of tezepelumab?

The main phase III study was NAVIGATOR, involving 1,061 patients with severe, uncontrolled asthma.[7] It was a 52-week exacerbation study, taking individuals across a broad spectrum of blood eosinophil count at entry, unlike many other comparable studies. The primary outcome measure was the annualized rate of asthma exacerbations in the overall population and in patients with a blood eosinophil count of less than 300 cells per microliter. There was a clinically and statistically significant decrease in exacerbations in both populations with tezepelumab

treatment compared to placebo of 56% and 41%, respectively. Secondary outcomes showed an early 2-week improvement in pre-bronchodilator forced expiratory volume in 1 second, as well as a statistically significant improvement in patient-reported outcome measures such as the asthma control questionnaire (ACQ-6) score and the asthma quality of life questionnaire (AQLQ). NAVIGATOR demonstrated that tezepelumab treatment improves a wide range of outcome measures in a broad population of patients with severe asthma.

Q: What is the safety profile of tezepelumab?

At the moment, the safety profile of tezepelumab appears to be good. We have the phase II and phase III study data, and there is a long-term extension study called DESTINATION (ClinicalTrials.gov Identifier: NCT03706079), which is yet to read out, but there have been no significant safety signals to date.[8] This will be kept under active review with post-marketing surveillance.

Q: What will be the impact of this approval on clinical practice?

This will have a significant impact on clinical practice for a number of reasons. The biologics that we have at the moment are effective for some patients but not for everyone, potentially because they target specific parts of the asthma inflammatory pathway. People often have a combination of allergic asthma and eosinophilic asthma and because tezepelumab has a broad mechanism of action it will be able to target both components. The impact on airway hyperactivity is also important. We know a lot about airways inflammation but we need to remember that airways hyperactivity is also important. Tezepelumab targets both inflammation and hyperactivity of the airways. Further studies are needed to determine where it best sits in the treatment of asthma, and whether we can start to think about other indications for tezepelumab, and other goals, for example, thinking beyond asthma control and looking towards asthma remission.

Q:Which patients are most likely to benefit from treatment with tezepelumab?

This is an important question. We now have six biologics and there are no direct head-to-head comparisons, so we decide which patients are most likely to benefit from treatment based on clinical intuition and the available study data. As I have discussed, tezelepumab's mechanism of action makes it suitable for a broad population of people with severe asthma. There is never going to be a single biologic that is the answer for everyone, but I suspect that this will become a logical first-line biologic treatment for many. It is important to stress that this is the first biologic that works in people irrespective of biomarkers. This is, therefore, the only treatment option for people with a low blood eosinophil count with non-atopic asthma. It may also be the right treatment for many patients who have a combination of allergic and eosinophilic asthma. Ongoing studies and clinical experience will help determine exactly where it should sit in our treatment regime. ❑

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