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**New paradigm in asthma management: switching between biologics!**

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The *nominalist* definition acknowledges asthma as an abnormality of the airways, typically comprising of variable airflow limitation over short periods of time, hyperresponsiveness and airway inflammation (1). The severity of asthma has primarily been assessed by the level of treatment required to control symptoms and exacerbations, with corticosteroids (inhaled and/or oral) as the mainstay treatment for suppressing the overall inflammatory component (2). It was not until the past decade that enough importance was given to the precise recognition, assessment and targeted treatment of inflammation in clinical asthma management. Indeed, in today's time and age, one can no longer state that. There are four monoclonal antibody (mAb) therapies (omalizumab, mepolizumab, reslizumab and benralizumab) that are currently approved as an adjunct therapy for targeting the inflammatory component of severe asthma. In fact, there are a few more in the pipeline for the same (dupulimab, tezepulimab, etc.) (reviewed extensively in (3)). This paradigm shift in clinical management of targeting the underlying inflammatory component, can be attributed to the identification of asthma "endotypes" from "phenotypes" (4) – an approach that integrated the underlying immunobiology of inflammation contributing to severity and the clinical manifestations as a consequence.

Broadly, there are two endotypes of asthma characterised as Type 2 (T2) high and T2 low inflammation (3). Biologics targeting mediators associated with T2 high inflammation in asthma have been hugely successful. For instance, identifying immunoglobulin (Ig) E as the dominant mediator of T2 inflammation in early onset allergic asthma led to the development of a targeted monoclonal antibody (mAb), omalizumab, that allows ~ 25% reduction in asthma exacerbation rates and substantial tapering of inhaled corticosteroid (ICS) maintenance doses. However, to date, its steroid-sparing effect in patients on daily oral corticosteroids (OCS) remains to be confirmed (5). Though omalizumab is approved for severe allergic asthma, retrospective analysis of 25 randomised controlled trials (RCTs) demonstrated greater reduction in asthma exacerbations in patients with high blood eosinophil counts and high exhaled nitric oxide levels, indicative of ongoing eosinophilic inflammation (6). Therefore, prescribing the available anti-IgE mAb to severe allergic eosinophilic asthmatics seemed justified when a targeted eosinophil-depletion strategy was unavailable to clinicians. More than a decade later, mepolizumab, an IgG<sub>1</sub> mAb targeting the

IL-5 pathway (crucial for the maintenance of the eosinophil biology), was approved for severe eosinophilic asthma (see Table 1 for clinical indications for both mAbs). RCTs reported a ~50% reduction in exacerbation rates, a decrease in total use of OCS, and complete weaning off OCS in 14% patients (3). Despite differences in the target molecule and mechanisms of drug actions, both mepolizumab and omalizumab are indicated as a Step 5 GINA treatment for severe eosinophilic asthma (2).

In the current study by Chapman *et al.*, published in this issue of the journal, encouraging efforts were made to investigate whether mepolizumab could optimally control a subset of moderate-to-severe eosinophilic asthmatics who were otherwise inadequately controlled on omalizumab. The open-label, single-arm, multicenter study was designed with a pragmatic approach of switching from one (omalizumab) to another biologic (mepolizumab) without a standard wash-out period (which is usually the scenario in clinical practise). The study was conducted in patients who were eligible for both biologics and had uncontrolled disease. The authors report substantial improvement in asthma control using Asthma Control Questionnaire-5 (ACQ-5) with 77% of asthmatics achieving the minimal clinically important difference (MCID, reduction by 0.5 points) at week 32, and also significant reduction of blood eosinophils and serum markers of eosinophil activation (eosinophil cationic protein).

The key finding of this study that can be immediately translated into clinical practise is the direct switch from omalizumab to mepolizumab (within 2-4 weeks of the last biologic dose) with no reported adverse/tolerability issues. Subgroup analysis confirmed no additional benefit when both biologics were in the patient's system, nor a decline in benefit as omalizumab was naturally washed-out in the second half of the study. It is apparent that the 111 patients (77%) who showed favorable clinical outcomes to mepolizumab had an underlying IL-5 mediated pathology, wherein curbing only the IgE component with omalizumab was inadequate. From a molecular stand-point, since IL-5 is upstream of IgE in the canonical allergic inflammatory cascade, coupled with current emerging evidence of non-IgE mediated alternative IL-5 pathways that can maintain eosinophilia, it is reasonable to expect an anti-IL-5 mAb to be effective when an anti-IgE mAb fails to curb symptoms. However, in the current study there is lacking information regarding strict eligibility for

omalizumab in the initial phase. This may be attributed to the fact that in the era of single use of omalizumab, the eligibility process may have overlooked a strict application of the initial recommendations.

With a number of mAbs currently available for treating severe asthma with a T2 high signature, it has become crucial to objectively assess biomarkers that would indicate the dominant inflammatory mediator driving disease symptoms in the target organ (i.e. the airways). In this study, it may be argued that selecting patients based on blood eosinophils (with an absolute count of 150-300 cells/ $\mu$ L) was adequate to predict and monitor response to mepolizumab. However, discordance between blood and sputum eosinophilia with increasing asthma severity (7), and reported incidents where mepolizumab response was deemed clinically inadequate despite normalisation of blood eosinophil levels (8, 9), question the reliability of blood eosinophils as the biomarker of choice. In fact, in the current study 41% patients experienced a total of 104 exacerbations within the 32-week study period, despite normalisation of blood eosinophil levels by week 8. Again, the median ACQ-5 score reported at week 32 was 1.75 (ACQ-5 <1.5 is considered to reflect asthma control), indicating that a sub-set of patients remained symptomatic. Further, we note that 5% (7) of the recruited patients experienced asthma worsening. This is in tandem with a recent report of asthma worsening on mepolizumab therapy in a prototype severe OCS-dependent asthmatic with persistent airway eosinophilia (9). It may be argued that assessing the “rate of exacerbations” would have been a more objective outcome to evaluate the optimal therapeutic effect of mepolizumab, especially in this patient set selected based on the evidence of exacerbations despite omalizumab therapy.

Clinical trials as such conducted by Chapman *et al.*, in a pragmatic clinical setting are required to assess the effectiveness of novel therapies indicated for a similar/overlapping asthma population, essentially when (i) one biologic is deemed clinically inadequate to control symptoms and, (ii) in the absence of head-to-head inferiority/superiority trials. It may have been prudent for the authors to assess clinical parameters (vital for identifying precise biomarkers) that could discriminate between patients who responded to omalizumab, from those who did not, and more importantly, those who went ahead and responded to mepolizumab. The future now warrants the identification and validation of

precise biomarkers that will present a better ability to predict response to mAb treatment either alone or in combination with existing therapies. In the meantime, the immediate unmet need in asthma clinical management can be summarized in one sentence: "selecting the right patient, recognizing the right target and focusing on the right outcome".

**Table 1: A comparative analysis between Omalizumab vs. Mepolizumab**

| Parameters                                    | Omalizumab                                                                                                                                                                                                                             | Mepolizumab                                                                                                                                                                                           |
|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Approval</b>                               | July 2003                                                                                                                                                                                                                              | November 2015                                                                                                                                                                                         |
| <b>Tradename</b>                              | Xolair <sup>®</sup>                                                                                                                                                                                                                    | Nucala <sup>®</sup>                                                                                                                                                                                   |
| <b>Biochemical make-up</b>                    | IgG <sub>1</sub> k mAb; 149 kDa                                                                                                                                                                                                        | IgG <sub>1</sub> k mAb; 149 kDa                                                                                                                                                                       |
| <b>Bioavailability and half-life</b>          | 62%                                                                                                                                                                                                                                    | 80%                                                                                                                                                                                                   |
| <b>Mean half-life (t<sub>1/2</sub>)</b>       | 26 days                                                                                                                                                                                                                                | 16-22 days                                                                                                                                                                                            |
| <b>Dosing regime</b>                          | 75 to 375 mg every 2 or 4 weeks. Dose (mg) and frequency is determined by serum total IgE level (IU/mL) and body weight (kg)                                                                                                           | 100 mg fixed dose every 4 weeks                                                                                                                                                                       |
| <b>Route of administration</b>                | Subcutaneous                                                                                                                                                                                                                           | Subcutaneous                                                                                                                                                                                          |
| <b>Patient population</b>                     | Severe to moderate asthma, positive allergy testing, incomplete control with daily corticosteroid therapy, elevated serum IgE; 6 years and older                                                                                       | Severe eosinophilic asthma inadequately controlled despite treatment based on GINA 4-5 steps, blood eosinophil level ≥ 150-300 cells/μL; 12 years and older                                           |
| <b>Reported clinical efficacy as per RCTs</b> | <ul style="list-style-type: none"> <li>• 25% reduction in exacerbations</li> <li>• steroid-sparing in ICS-dependent asthmatics, while minimal evidence of the same in OCS-dependent sub-set</li> </ul>                                 | <ul style="list-style-type: none"> <li>• ~50% reduction in exacerbations</li> <li>• decreases total use of OCS, and complete weaning of OCS in 14% of patients</li> </ul>                             |
| <b>Adverse Reactions</b>                      | Anaphylaxis reported in 0.1% of asthma patients in RCTs                                                                                                                                                                                | Hypersensitivity reactions and opportunistic infections (herpes zoster)                                                                                                                               |
| <b>Mechanism of action</b>                    | <ul style="list-style-type: none"> <li>• Binds to IgE and prevents the subsequent binding to its receptor (FcεRI) on mast cells, basophils, eosinophils, and dendritic cells and limits immediate allergic mediator release</li> </ul> | <ul style="list-style-type: none"> <li>• Binds to IL-5 ligand and prevents its binding to the alpha chain of the IL-5 receptor and thereby inhibits production and survival of eosinophils</li> </ul> |

\*N.B. RCT = randomised controlled trials; ICS = inhaled corticosteroid; OCS = oral corticosteroid (prednisone); IU – international units; approval date is based on that by the US Food and Drug Administration; information summarized from <https://www.accessdata.fda.gov> (accessed 05/05/2019)

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