TREATING INADEQUATELY CONTROLLED ASTHMA: EXPLORING THE POTENTIAL OF PHENOTYPE-TARGETED THERAPY

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MEETING SUMMARY

Asthma is inadequately treated with the current standard of care. This session aimed to explore the potential of a phenotype-targeted approach to asthma management, which would allow a more tailored approach to treatment and result in better clinical outcomes for difficult-to-treat patients. Evidence was presented indicating that eosinophils play an important role in the pathogenesis of asthma. The importance of anti-interleukin (IL)-5 therapies, with the focus on therapies currently in development and their potential clinical benefit for the eosinophilic asthma phenotype, was also explored.

Inadequately Controlled Asthma: The Unmet Needs and Impact on Asthma Management

Professor Ratko Djukanovic

Asthma is a heterogeneous disease with many phenotypes. The Global Initiative for Asthma (GINA) lists a number of asthma phenotypes, including allergic asthma, non-allergic asthma, late-onset asthma, asthma with fixed airflow limitation, and asthma with obesity,[1] although a clearly defined phenotype is not in use in routine clinical practice.

Over the past few years, significant progress has been made to define asthma phenotypes more clearly. Stimulation of airway epithelial cultures from healthy individuals and patients with mild-to-moderate asthma with IL-13 revealed overexpression of the biomarkers periostin, CLCA1, and SerpinB2 in only a proportion of asthmatics, leading to the definition of two groups of patients: T-helper type 2 (Th2)-high and Th2-low.[2] Patients

with Th2-high genotype expression had a higher number of eosinophils in their peripheral blood and in their bronchoalveolar lavage fluid.[2] Other features of Th2-high asthmatics include higher serum immunoglobulin E (IgE) concentrations, more positive skin prick tests, higher expression of the mucins MUC5AC and MUC5B, and a thicker basement membrane.[2] The clustering of genes induced by Th2 cytokines, coupled with the readily measurable features of asthma, in particular eosinophils, may help to define a clearer asthma phenotype and how this is related to a specific biological mechanism.

Using topological data analysis (TDA), which creates topological networks revealing statistically significant patterns of complex data, a recent study of asthmatics demonstrated that individuals with mild, predominantly steroid-naïve asthma had elevated Th2 cytokines (IL-13, IL-4, and IL-5).[3] Two clusters of patients were identified as having severe asthma: one cluster consisted of individuals who were older, obese, and atopic, with upregulated Th2 cytokines and mast cell mediators. The second cluster consisted of individuals who were obese, non-atopic, female, and also had raised mast cell mediators, a finding that was unexpected (Figure 1).[3]

Further characterisation of patients has been undertaken in the Unbiased BIOmarkers in PREDiction of respiratory disease outcomes (U-BIOPRED) study, a public/private partnership dedicated to applying systems biology to develop new preclinical models of asthma to advance drug development for severe disease.[4] Multiple sample types were analysed in the study using 'omics' methods, clustering the data by standard methods as well as TDA to identify 'fingerprint' biomarkers, with the aim of combining them to determine a few biomarkers identifying particular phenotypes.

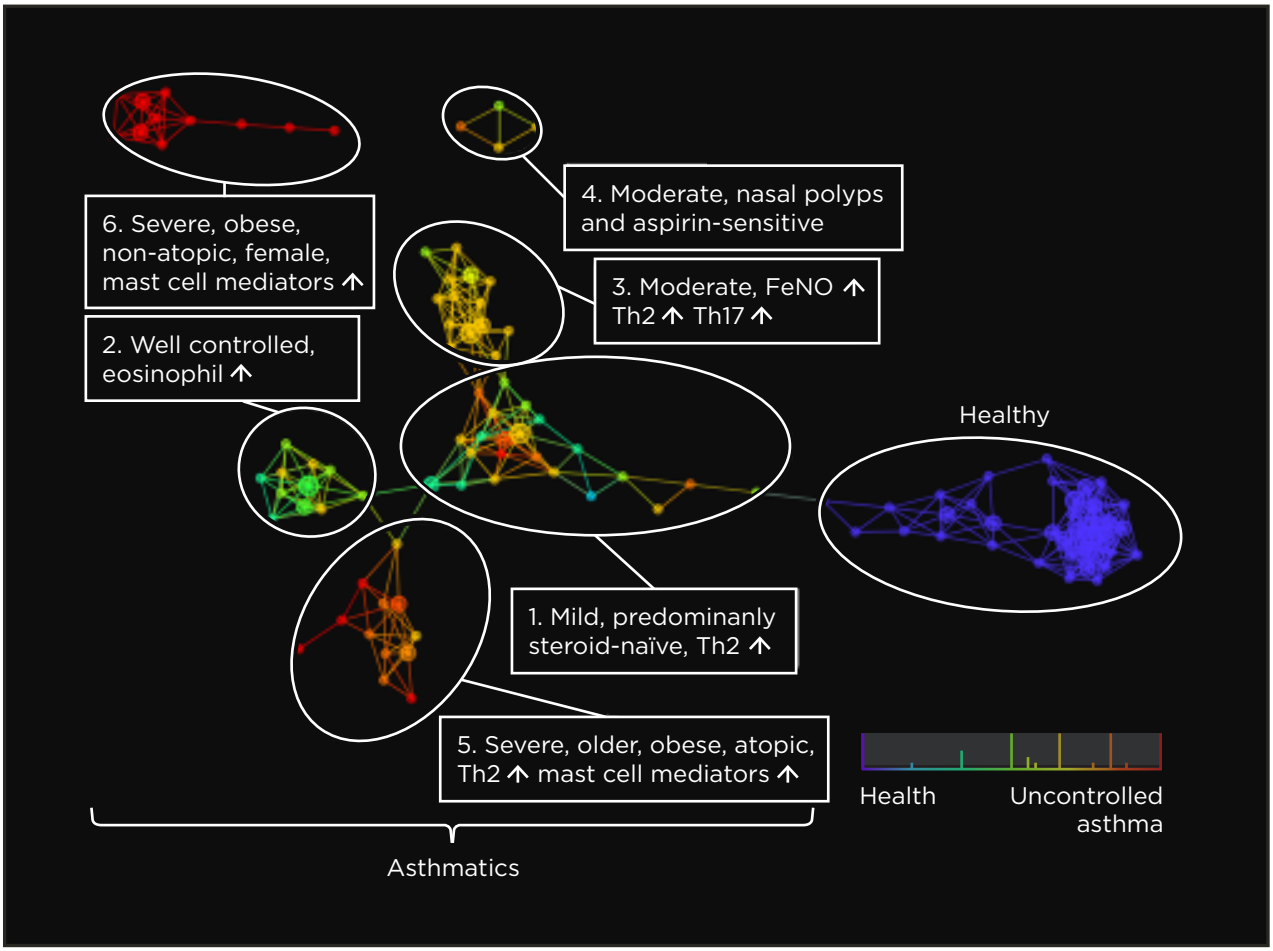

Figure 1: Multi-dimensional clinico-pathobiological clusters in asthmatic patients and healthy individuals.[3] The network is coloured according to disease severity (GINA classification), with patients with the most severe disease in red and patients with the milder forms in varying shades of orange, yellow, and green. FeNO: fractional exhaled nitric oxide; Th2: T-helper type 2; Th17: T-helper type 17.

Mass spectrometry was used to analyse proteins in sputum samples from asthmatic patients, and TDA was applied to these results, revealing 10 clusters of asthma. Three clusters representing more severe asthma were highly eosinophilic and could be identified as being three subtypes of eosinophilic asthma.[4] When blood biomarkers were investigated as indicators of biomarkers in sputum samples, periostin was found to be a good biomarker for inflammation in patients with eosinophilia in sputum.[4]

It is hoped that the findings from the U-BIOPRED study will help to provide a more granular definition of asthma, one that may allow determination of which phenotypes of the disease are responsive to specific biologics. The use of these sophisticated tools will potentially allow a more stratified approach to treatment, leading to the development of drugs that are safer and more effective, resulting in better and more economical healthcare.

Treating Inadequately Controlled Asthma: the Role of the Eosinophil

Professor Michael Wechsler

Currently available therapies for asthma include short and long-acting beta-agonists, inhaled corticosteroids (ICS), leukotriene modifiers, anti-IgE, systemic steroids, immunotherapy, anticholinergics, bronchial thermoplasty, and allergy immunotherapy. However, these treatments do not offer patients personalised therapy and, despite the widespread adoption of guideline-based approaches (including the National Asthma Education and Prevention Program[5] and the GINA guidelines),[1] in many patients asthma remains poorly controlled and associated with significant morbidity.

A more personalised approach to treatment would involve identification of different phenotypes, including gender, age, obesity, ethnicity/race, smoking history, and early versus late-onset asthma; however, this approach can sometimes be non-specific. Identification of endotypes, such as levels of blood and sputum eosinophils and immunoglobulins as well as neutrophils, may offer a more specific approach to treatment that allows the targeting of a mechanistic pathway.[6] Ideally, tailoring treatment using pharmacogenetics would allow for an even more individualised approach to asthma therapy.

Asthma is complex and heterogeneous. One paradigm of asthma pathogenesis involves allergens stimulating Th2 cells to release a variety of cytokines that act on different cells to mediate the inflammatory response. The development of asthma therapies is evolving to target specific aspects of the allergic cascade. One such cell is the eosinophil, which has recently been discovered to have an important role in the pathogenesis of asthma and releases a number of cytokines that contribute to the chronic inflammatory process, including IL-5.

Around 40–60% of asthma is classified as eosinophilic[7] and is often associated with symptom severity.[8] A study of non-invasive markers of inflammation in sputum, resulting from exacerbations induced by a reduction in ICS therapy, demonstrated that exacerbations developed in 7 patients (N=15) over 8 weeks and were associated with an increase in baseline sputum eosinophils.[9] The same study found a decrease in peak expiratory flow variability and forced expiratory volume in 1 second (FEV_1) in relation to eosinophilia.[9] Similarly, a study that measured the expression of two markers of eosinophil activity in mucosal eosinophils, eosinophil cationic protein and major basic protein, found that these increased when ICS therapy was withdrawn.[10]

Analysis of data from the National Health and Nutrition Examination Survey (NHANES), an annual cross-sectional survey of the US general population, provided a further link between eosinophilia and exacerbations. Results across 2001–2010 surveys found that 3,162 patients with asthma had blood eosinophil data. Of these, 56% of children and 53% of adults had a self-reported asthma attack in the previous year, with elevated blood eosinophil counts (≥300 cells/μL) being associated with more self-reported asthma attacks compared with lower eosinophil counts.[11] In the PREDictors of UNcontrolled Asthma (PREDUNA) study, adult patients with asthma and eosinophil levels ≥400 versus <400 cells/μL in 2010 had significantly increased asthma exacerbations, emergency department visits, and excessive short-acting β_2-agonist dispensing in 2011.[12]

Results from these studies demonstrate that there is an increased number of eosinophils in allergic symptomatic asthma, particularly when ICS therapy is withdrawn, ultimately leading to airway hyperresponsiveness.

In the last 10–15 years, evidence has emerged suggesting that asthma management can be guided by sputum eosinophil count.[13] When patients with moderate-to-severe asthma were given ICS therapy titrated according to the British Thoracic Society guidelines[13] or according to changes in their sputum eosinophil counts,[14] it was observed that, although ICS therapy was similar in the two groups, there was a 50% reduction in exacerbations in individuals who had their asthma managed based on sputum eosinophils.[13]

It is clear that eosinophils play an important role in the pathogenesis of asthma in a large proportion of patients, with the degree of eosinophilia being associated with a greater degree of exacerbations. Targeting eosinophils with inhaled and systemic corticosteroids and with anti-IL-5 therapy results in a reduction in exacerbations. The availability of newer, more specific biomarkers for asthma severity will facilitate better mechanism-focussed management of this disease in the future.

The Clinical Benefits of Reducing IL-5 Signalling Among Inadequately Controlled Asthma Patients: The Latest Evidence

Professor Mario Castro

There are a number of potential phenotype-targeted therapies in severe asthma, in particular treatments targeting eosinophilic asthma that include anti-IL-5, anti-IL-4, anti-IL-13, and IL-4α.[15] Recently, greater understanding of the role of the eosinophil in driving the pathobiology of asthma has emerged,[16] along with evidence that targeted treatment of this phenotype is beneficial, particularly in patients with difficult-to-treat asthma.

Eosinophils release several mediators that have effects on the epithelium, fibroblasts, smooth muscle, mast cells, and Th2 cells, and in combination lead to airway hyperresponsiveness and remodelling. Evidence implicating IL-5 in asthma includes the increased expression of IL-5 mRNA in bronchial biopsies taken from patients with asthma compared with non-asthmatic controls, and increased IL-5 mRNA following bronchial provocation with allergen in patients with asthma.[17] Furthermore, inhalation of recombinant human IL-5 leads to increased eosinophilia in induced sputum and in airway hyperresponsiveness.[18]

Several interdependent determinants of anti-IL-5 response in asthma include blood and airway eosinophils, exposure to drug therapies (e.g. ICS), disease severity, and other factors such as associated comorbidities and allergies. Understanding these key factors will allow targeted treatment currently active tissue eosinophilia, as well as prevention of the influx associated with future exacerbations.

Initial clinical results for the investigational anti-IL-5 therapy mepolizumab (750 mg or placebo) in 24 unselected patients with mild asthma revealed that, despite a clear reduction in blood eosinophil levels, there were no changes in clinical outcomes of asthma in these patients.[19] A larger study included 362 unselected patients with asthma on ICS therapy who received intravenous (IV) mepolizumab and, similarly, although there was a significant reduction in blood and sputum eosinophils in both groups, there were no statistically significant differences in any of the clinical endpoints measured.[20] However, when the same therapy was used in selected patients with severe asthma with persistent sputum eosinophilia (median sputum eosinophils in placebo group: 4.0%, range: 1.6–4.3%; in mepolizumab group: 16.6%, range: 0–35.3%) despite oral prednisone (5 monthly infusions of IV mepolizumab 750 mg), there was a reduction in exacerbations, with 10 exacerbations in the placebo group and 2 exacerbations in the mepolizumab group (p=0.008). A single infusion of mepolizumab was associated with a significant reduction in sputum (p=0.005) and blood (p=0.004) eosinophils versus placebo. Although there was no significant reduction in FEV_1, there was a significant improvement in the Asthma Control Questionnaire (ACQ) scores.[21] These results were confirmed in a trial of 61 patients with persistent eosinophilic asthma who had ≥2 exacerbations and who were treated with mepolizumab (750 mg, monthly) for 12 months. A decrease in cumulative exacerbations and a significant reduction in blood (p<0.001) and sputum (p<0.002) eosinophils occurred,[22] highlighting the importance of selecting the correct patients for anti-IL-5 therapy.

In the DREAM trial, carried out in a much larger cohort than the previous trials, 621 patients were randomised to receive placebo or mepolizumab (75, 250, or 750 mg) at 4-week intervals.[23] IV mepolizumab 750 mg significantly reduced the number of asthma exacerbations in patients with severe eosinophilic asthma compared with placebo (52% reduction, range: 36–64%; p<0.0001), and

lowered blood and sputum eosinophilic counts. There were small effects of mepolizumab on FEV_1 and Asthma Quality of Life Questionnaire (AQLQ) and ACQ scores, but these did not differ significantly from placebo and the overall frequency of serious adverse events was similar across treatment groups.[23]

A new anti-IL-5 therapy not currently licensed for the treatment of asthma, reslizumab, has been trialled in patients with elevated eosinophil counts (induced sputum eosinophils ≥3%). Although reslizumab (IV 3 mg/kg) in patients with poorly controlled eosinophilic asthma did not result in a statistically significant improvement in baseline ACQ score, FEV_1 did significantly improve from baseline after 4 weeks (p=0.0364); this rapid improvement was sustained after 16 weeks (p=0.0025).[24] When looking at a subgroup of patients who had a history of nasal polyps, there was a profound improvement in the ACQ score from these patients.

Two multi-centre, parallel, double-blind, randomised, placebo-controlled, Phase III trials assessed the efficacy and safety of reslizumab (IV 3 mg/kg) in patients with inadequately controlled, moderate-to-severe asthma over 52 weeks.[25] Both trials had similar demographics, with similar corticosteroid use and a mean blood eosinophil count of 610–696 cells/μL. In both studies, patients receiving reslizumab displayed a significant reduction in the frequency of asthma exacerbations compared with those receiving placebo (Study 1 rate ratio [RR]: 0.50, 95% confidence Interval [CI]: 0.37–0.67; Study 2 RR: 0.41, 95% CI: 0.28–0.59; p<0.0001 for both studies). An improvement in FEV_1 with reslizumab versus placebo was seen in both trials by the first on-treatment assessment at Week 4 and was sustained through to Week 52 (0.11 L, 95% CI: 0.067–0.15; p<0.0001). Pooled sub-analyses showed increasing mean FEV_1 improvements with increasing disease severity on the basis of background medication, which was most evident at 52 weeks (0.081 L, 95% CI: −0.02 to 0.18 for ICS; 0.113 L, 95% CI: 0.06 to 0.16 for ICS plus long-acting beta-agonists; and 0.151 L, 95% CI: 0.02 to 0.290 for oral corticosteroid-dependent patients).[25] Compared with placebo, reslizumab treatment also resulted in significant improvements in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index score, and was associated with a reduction in blood eosinophil counts. The overall safety profile of reslizumab was similar to that of placebo.[25] These early results in eosinophilic asthma show that reslizumab can be targeted to the patients with blood eosinophil counts of 400 cells/μL who have inadequately controlled severe asthma on current therapy. However, it must be noted that there are different definitions of eosinophilic asthma between mepolizumab and reslizumab trials, with blood eosinophil counts ranging between 150 cells/μL (mepolizumab) and 400 cells/μL (reslizumab).[25]

Another targeted anti-eosinophil therapy, benralizumab, is currently under investigation. Benralizumab is a humanised, afucosylated monoclonal antibody that binds to the α subunit of the IL-5 receptor and depletes eosinophils through antibody-dependent cell-mediated cytotoxicity.[26] In the initial open-label, single, dose-escalation study of benralizumab, IV doses (0.0003–3 mg/kg) were administered to 44 patients with mild atopic asthma over approximately 3–30 minutes. Results showed that mean peripheral blood eosinophil levels decreased in a dose-dependent manner and eosinophil cationic protein levels were reduced from 21.4±17.2 μg/L (baseline) to 10.3±7.0 μg/L (24 h post-dose).[27] When the effect of benralizumab on sputum eosinophils was investigated, it was found that, when administered intravenously (1 mg/kg) or subcutaneously (SC, 100 mg or 200 mg), benralizumab significantly reduced the percentage of sputum eosinophils in asthmatic patients.[28]

An additional study used a mathematical algorithm that predicts sputum eosinophils from complete blood count to select patients according to their phenotype. Non-eosinophilic patients were randomised to placebo or benralizumab (SC 100 mg) and eosinophilic patients were randomised to placebo or three doses of benralizumab (SC 2 mg, 20 mg, or 100 mg).[29] The primary results showed that, in the eosinophilic group, there was a significant rate reduction in the exacerbation rate with benralizumab 100 mg versus placebo (0.34 versus 0.57, 41% reduction, 80% CI: 11–60; p=0.096), but not in the 2 mg or the 20 mg group. In patients with a baseline blood eosinophil cut-off of at least 300 cells/μL, exacerbation rates in the benralizumab group were lower than in the placebo group (20 mg: 0.30 versus 0.68, 57% reduction, 80% CI: 33–72, p=0.015; 100 mg group: 0.38 versus 0.68, 43% reduction, 80% CI: 18–60, p=0.049). There was also a significant improvement in FEV_1 in the non-eosinophilic group and the eosinophilic group at all doses, as well as in patients with baseline blood eosinophils ≥300 cells/μL.[29] ACQ-6 scores significantly improved in eosinophilic and non-eosinophilic patients and in patients with baseline

blood eosinophils ≥300 cells/μL treated with benralizumab at all doses.[29] Treatment-emergent adverse events occurred in 277 (72%) of 385 participants receiving any benralizumab dose, compared with 143 (65%) of 221 receiving placebo. Most adverse events were mild-to-moderate in severity, indicating that benralizumab had an acceptable safety profile at all doses.[29]

These early Phase IIb findings show the potential of benralizumab in treating difficult-to-treat patients and support further clinical development of benralizumab as a potential novel anti-IL-5 therapy that may affect exacerbations, lung function, and be of clinical benefit to patients with uncontrolled eosinophilic asthma.

Q&A session

Do patients migrate from one endotype to another depending on the time of sampling?

Prof Djukanovic replied that they probably do not, although this may be dependent upon the intensity of the endotype. Some evidence has shown that levels of sputum eosinophils measured over 1 year were enormously variable. Prof Wechsler added that the endotype is probably fluid and is likely to change depending on the therapy. Blocking Th2 pathways resulted in the animal model switching to a non-Th2 phenotype of asthma, but blocking both of these pathways resulted in better outcomes.

How variable are eosinophil counts? Is variability the same with peripheral eosinophil counts and sputum eosinophil counts? Is more than one analysis required?

Prof Djukanovic replied that sputum eosinophil counts vary, but blood eosinophil counts have not been studied in as much detail. However, it is thought that these are relatively stable. Essentially, this is because the homeostatic mechanisms are less stable in the lungs than they are in the blood. It is important to consider that there is a limited amount of information that has determined that blood eosinophil counts are more stable than sputum eosinophil counts.

What would be the best choice between an anti-IL-5 and an anti-IgE therapy for asthma patients who are atopic and have high eosinophils?

Prof Wechsler stated that there have been no head-to-head studies comparing anti-IgE and anti-IL-5 therapy. Given the specificity for eosinophils, anti-IL-5 would be preferred in eosinophilic asthma. However, some evidence has shown that patients with higher eosinophil counts responded better to anti-IgE therapy. There is a need for a clinical trial that compares biologics head-to-head.

Are exacerbations and lung function improvement related and/or unrelated? And because of the underlying cause in the eosinophils, what type of mechanistic hypothesis do you propose to explain this difference amongst the anti-IL-5 therapies?

Prof Castro replied that it is clear that biologic inhibition of IL-5 has an anti-eosinophilic and anti-inflammatory mechanism, although the evidence is limited about whether this translates to an improvement in airflow. Prof Djukanovic added that there needs to be a head-to-head comparison of the various anti-IL-5 therapies. The higher the eosinophil count then the better the clinical effect. Prof Wechsler also added to the discussion by stating that there is currently an ongoing study in 135 patients with eosinophilic granulomatosis with polyangiitis treated with reslizumab or placebo. This will hopefully confirm results from previous studies that have shown that reslizumab significantly reduces exacerbations and reduces steroid dosing by 75%. The study should be completed next August and results will probably be available by the time of the ERS congress next year.

Is there a flaw in anti-IL-5 therapy?

Prof Djukanovic answered by stating that if the accumulation of eosinophils is not dependent on IL-5 then anti-IL-5 therapy will not work.

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