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Much ado about Biologicals: *Highlights of the Master Class on Biologicals, Prague, 2018*

To the Editor,

Novel insights into the interactions between our genome, exposome, and innate and adaptive immunity underlying asthma and allergic disease prompted the development of targeted treatments including biologicals and small molecules (Figure 1). These novel agents may revolutionize the treatment of asthma and related conditions, but simultaneously impose challenges on physicians and researchers. These topics were addressed in the Master Class on "Personalized treatments of chronic inflammatory upper and lower airways disease: biologicals, immunomodulators and other targeted therapeutics," organized by the sections Asthma, ENT, and Immunology of the European Academy of Allergy and Clinical Immunology (EAACI).

Interactions exist between environmental factors, including air pollutants, allergens, viruses, and the microbiome, and our immune system. Mucosal surfaces provide barrier and interface functions, while the epithelium itself can be subject to functional adaptation based on microenvironmental cytokine profiles. Dendritic cells (DCs) migrating between epithelium and lymph nodes present antigens to T cells and thus elicit systemic immune responses or tolerance to antigen. Likewise, innate lymphoid cells 2 (ILC2) contribute to type 2 (T2) responses by rapid production of IL-5 or IL-13 and, similar to DCs and T cells, also respond to epithelial alarmins (TSLP, IL-25, IL-33). Adaptive responses enable individual immunological memory and advanced target repertoires using T cells and B cells, including

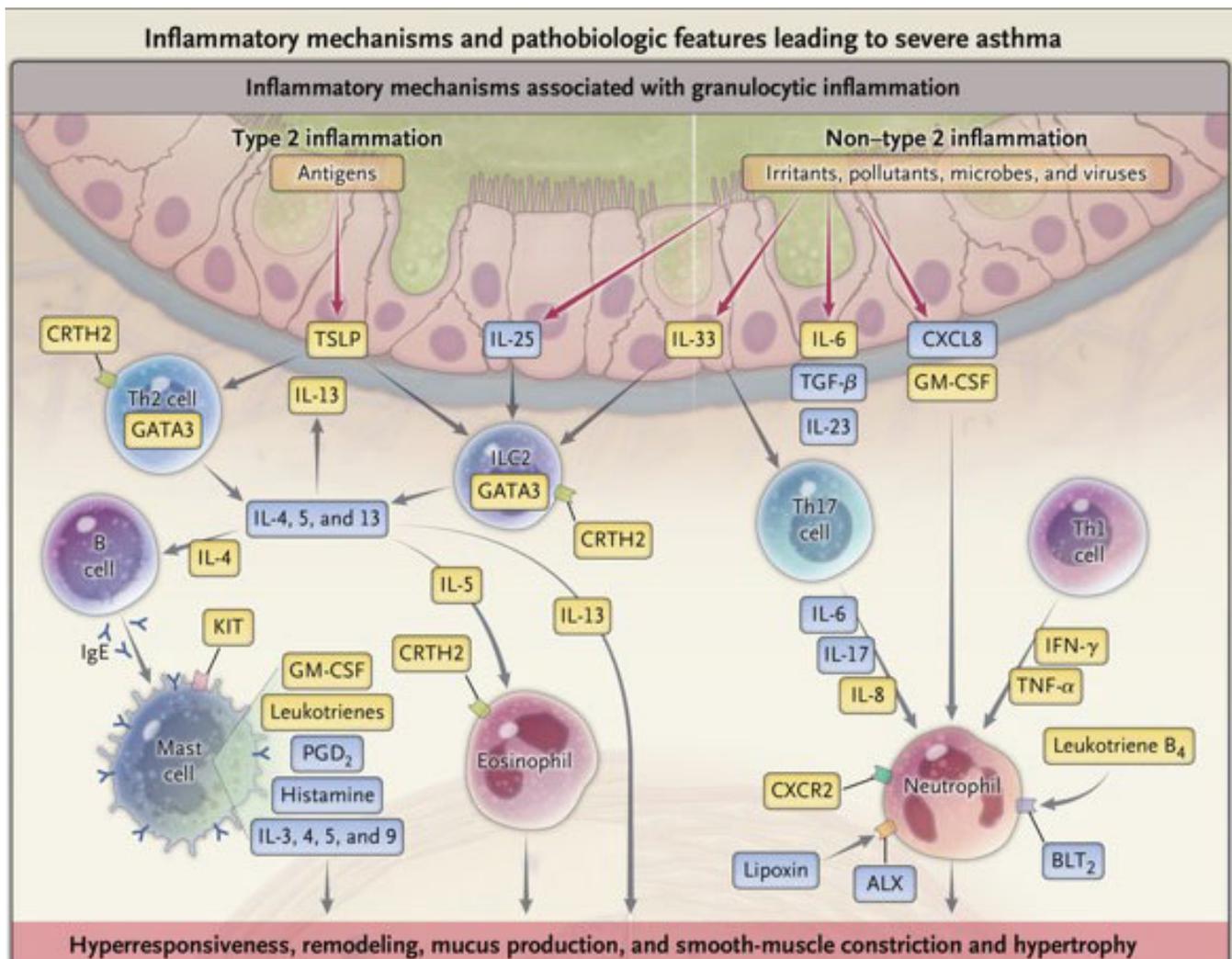


FIGURE 1 Current concepts on inflammatory pathways underlying asthma endotypes³

cytotoxic responses and antibody production. However, these mechanisms are also interlinked to, for example, complement responses and granulocytic responses. In allergic disease, IgE antibodies provide an antigen-specific stimulus to innate mast-cell responses.¹

Current evidence shows strong associations between the composition and metabolic activity of the microbiome present in the gut and on mucosal surfaces and the development of allergic disease and asthma.² The potentially detrimental effects of antibiotic use on resident microbial communities are an important topic for future research, and microbiome replacement and recovery protocols may be required in clinical practice following antibiotic therapy.

Identifying patients who may benefit from targeted treatment is an ongoing quest. Airway inflammation in asthma may be eosinophilic, neutrophilic, mixed-granulocytic, or paucigranulocytic. Eosinophilic inflammation is usually a T_H2-driven process, and therefore, sputum eosinophilia of $\geq 3\%$ usually indicates a response to treatment with glucocorticosteroids (GCS) or novel therapies targeted against T_H2-cytokines (IL-5, IL-4, IL-13).³ Similarly, chronic rhinosinusitis with nasal polyps (CRSwNP) represents a T_H2-inflammatory disease with promising response to targeted biologicals.⁴

Glucocorticosteroids are the cornerstones of asthma, CRSwNP, and atopic dermatitis treatment. However, clinical response to GCS may vary both across and within patients, and different factors can alter the GCS-induced signaling pathways leading to "GCS subsensitivity," which has been associated with dysregulated expression of glucocorticoid receptor isoforms, neutrophilic inflammation/Th17 cytokines, oxidative stress with downstream effects on histone deacetylase (HDAC) activities, and gene expression. Recently reported mechanisms inducing GCS insensitivity implicate the following: GCS-induced dysregulation of key transcription factors involved in host-defense, airway infections altering expression of critical regulatory elements, and autoimmunity in the airway triggered by the immunogenicity of eosinophil or neutrophil degranulation products.⁵ Kinase pathways may also be critical in mediating GCS insensitivity. Novel strategies targeting these mechanisms may provide alternatives to biologics targeting the T_H2 cytokines that are not suppressed by GCS in severe asthma.

For T_H2 severe asthma, there are several options (Figure 2).⁶ In patients with eosinophil-dominant T_H2 asthma, monoclonal antibodies (MoAbs) that target IL-5 (eg, mepolizumab and reslizumab) or the IL-5 receptor (eg, benralizumab) showed clinical effectiveness including

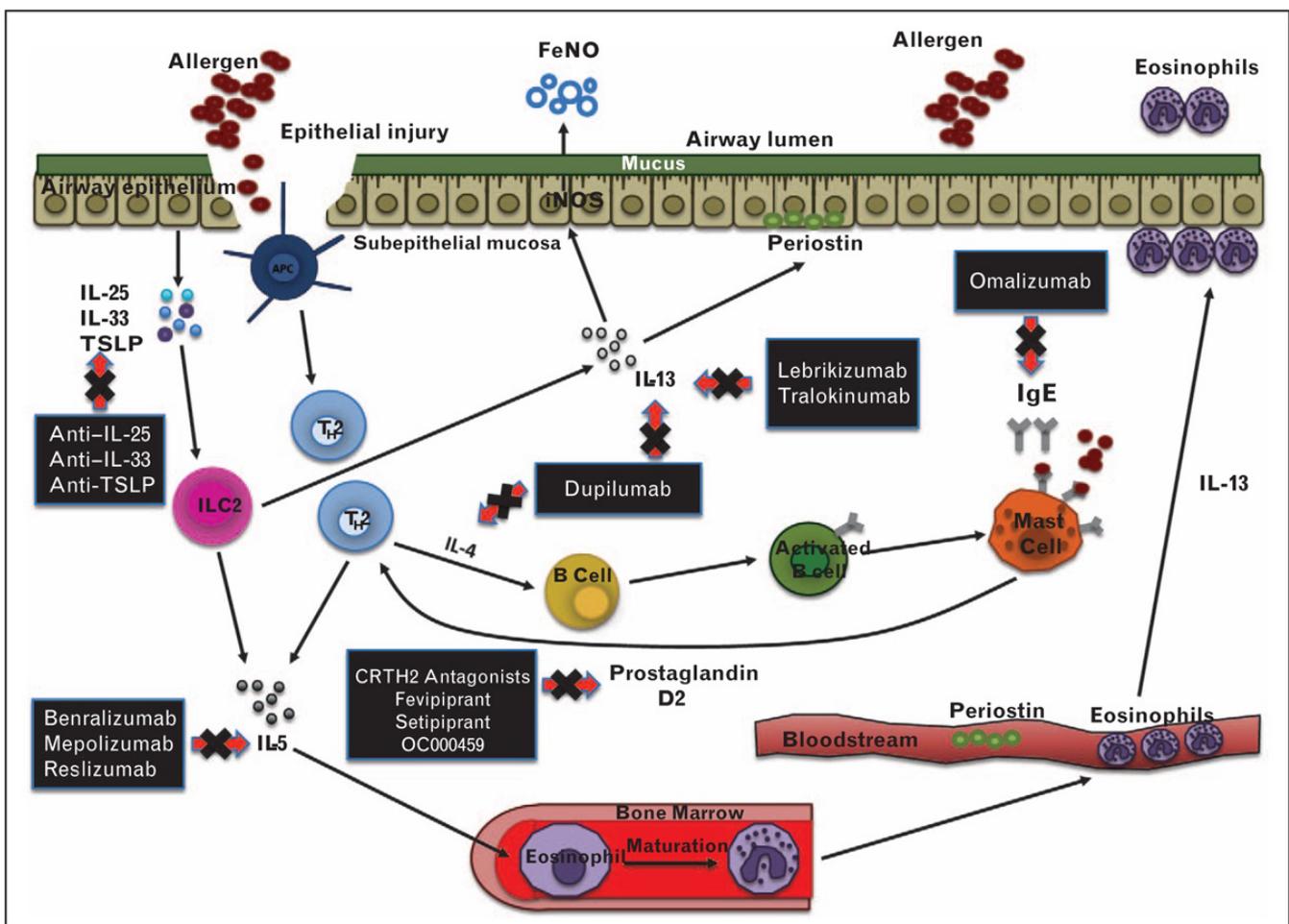


FIGURE 2 Targets, biomarkers and targeted options for T_H2 asthma.⁶ Please note that mepolizumab and reslizumab target IL-5, while benralizumab targets the IL-5 receptor

GCS-sparing properties, while small molecules that target CRTH2 may offer a practical and less expensive future alternative.³ Phase 3 studies with CRTH2 antagonists are ongoing including reflections on which patients may profit, while comparative studies with biologicals (eg, anti-IL-5) will be needed.

While characterization of “an eosinophilic phenotype” with blood or sputum is probably not critical in asthma patients who are not on daily prednisone, sputum eosinophils are a better biomarker of response to anti-IL-5 MoAbs than blood eosinophils in prednisone-dependent patients. In these patients, low doses of anti-IL-5 MoAb guided by blood eosinophils showed less efficacy than higher doses of anti-IL-5 and anti-IL-5R MoAbs. No head-to-head comparisons have been made. While anti-IL-5 therapies are effective in eosinophilic severe asthma independent of atopy, anti-IgE MoAb may be effective in those patients with a clear allergic component, although GCS-sparing effects have not been convincingly demonstrated. Serum IgE is not a good biomarker of response to anti-IgE therapies. Alternatively, T2 severe asthma with high FeNO levels and mucus in the airway might benefit from IL-4/IL-13 targeted therapy, irrespective of eosinophil counts.⁷ Targeting alarmins (eg, TSLP, IL-33) and kinases (eg, JAK) seems promising, and the results of phase 3 studies are awaited.³

Non-T2 asthma can present with sputum neutrophilia, which is generally a predictor of response to antibiotics and intense neutrophilia (associated with raised sputum total cell counts), unless proven otherwise, is often a response to an unrecognized airway infection. Trivial neutrophilia (increase in neutrophil % with a normal total cell count), in most patients, may reflect the high doses of GCS used to suppress T2 inflammation.³ Therefore, targeting neutrophil pathways with MoAbs against TNF, IL-1, IL-6, IL-8, IL-23, and IL-17 was unlikely to be clinically effective. Paucigranulocytic asthma may present with a fixed bronchoconstriction and/or airway hyperresponsiveness. These patients may benefit from smooth muscle-directed therapies including bronchodilators, bronchial thermoplasty (BTP), or mast-cell-directed therapies.⁷ Although clinical effectiveness has been shown for several asthma comorbidities, including allergic rhinosinusitis, chronic rhinosinusitis with nasal polyps (CRSwNP), so far most T2 targeted therapies are only registered for asthma or skin allergies.

In CRSwNP, biologicals are emerging therapeutic options, as recent evidence suggests major clinical benefits of IgE, IL-5, and IL-4/IL-13 targeted treatments.⁴ The majority of responders not only showed a reduction in nasal polyp size, but also a restoration of smell and overall well-being.⁴

Children represent a special population when considering targeted treatments, since distinct asthma phenotypes might be present in this population compared to adults. Currently, only anti-IgE and anti-IL-5 MoAbs have been approved as add-on treatment in children with poorly controlled asthma and there is little experience with biologicals in this population.

Considering the option of allergen immunotherapy (AIT), current evidence suggests that both subcutaneous (SCIT) and sublingual immunotherapy (SLIT) are efficient for allergic rhinitis and asthma,

although differences in some aspects are present. The differences are small, and no head-to-head comparisons are available.⁸

The lack of validated, clinically applicable biomarkers or composite markers allowing to adequately predict and monitor the (longitudinal) response to targeted treatments represents an important unmet need. Embracing the concept of unbiased multidimensional endotyping to address the complexity and dynamics of asthma is desired to move the field forward.⁹

CONFLICTS OF INTEREST

Diamant: works in CRO (QPS-NL) performing early-phase clinical studies for biotech/pharma companies and in past 3 years received honoraria for consultation and/or advisory boards from Acucort, Aquilon, ALK, AstraZeneca, Boehringer Ingelheim, Gilead, HAL Allergy, MSD, and Sanofi Genzyme. Vijverberg, Agache, Bjermer, Chaker, Gevaert, and Hellings: declared none. Nair: has received grants for investigator-initiated studies from AZ, Teva, Sanofi, Roche, BI, Novartis, and GSK and has participated in scientific advisory boards and meetings supported by Teva, Sanofi, Merck, AZ, Roche, Merck, Theravance, and Knopp. O'Mahony: has received a research grant from GSK and is a consultant to Alimentary Health Ltd. Panzner: participated in advisory boards supported by Novartis, GSK, and TEVA and in last 3 years received speaker fees from Novartis, TEVA, Boehringer Ingelheim, and Stallergenes Greer. Pohunek: participated in advisory board supported by Novartis, GSK, and TEVA and in last 3 years received speaker fees from Novartis, TEVA, Boehringer Ingelheim, and Stallergenes Greer. Vasakova: participated in scientific advisory boards supported by Teva, GlaxoSmithkline, and Novartis dedicated to biologic treatment of asthma.

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