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LETTER TO THE EDITOR

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Biologicals in allergic diseases and asthma: Toward personalized medicine and precision health: Highlights of the 3rd EAACI Master Class on Biologicals, San Lorenzo de El Escorial, Madrid, 2019

To the Editor

Biologicals have transformed the way of treatment of many immune-mediated disorders including cancer, autoimmune, and allergic diseases.[1,2] Biologicals and the understanding of their impact on diseases is a rapidly evolving field in which emerging important questions arise. Decisions on when to prescribe biologicals, how to develop clinical tools to elaborate an accurate endotype-based diagnosis and treatment approaches, how to identify and manage adverse and hypersensitivity reactions (HSR), and how to use biologicals in pregnancy, children, or elderly require additional research and evidence-based recommendations. All these aspects and other timely hot topics were addressed in the 3rd Master Class on Biologicals organized by the Biologicals Working Group and the Basic and Clinical Immunology Section of the European Academy of Allergy and Clinical Immunology (EAACI) in May 2019 in San Lorenzo de El Escorial, Spain.

Biologicals are products of high molecular weight that may be produced by living organisms, used to diagnose, prevent, and treat different diseases. Among them, monoclonal antibodies (mAbs) against specific targets are suitable for precision medicine as they bind to specific epitopes with high affinity, thus ensuring safety and efficacy. Biologicals provide therapeutic options when conventional approaches fail and contribute to our knowledge on the molecular mechanisms underlying complex diseases. In the era of precision medicine, personalized treatments are expected to allow a better selection of responders using well-defined biomarkers and might offer the opportunity to stop disease progression.[1,2] Several biologicals are approved or under development for the treatment of different atopic diseases in which type 2 immune-mediated mechanisms are predominant such as asthma, atopic dermatitis (AD), food allergy (FA), eosinophilic esophagitis (EoE), chronic rhinosinusitis with nasal polyps (CRS/wNP), and chronic urticarial (CU) (Figure 1 and Table 1). Detailed knowledge on the different disease endotypes using well-defined biomarkers is crucial to select the optimal targeted treatment for each patient.[1-3]

The management and treatment of skin diseases such as AD and CU experienced significant advances with the introduction of new biologicals. IL-4 and IL-13 signaling pathways play a key role in the pathophysiology of AD. Dupilumab, a mAb targeting IL-4Rα chain, shared by IL-4 and IL-13 receptors, demonstrated great efficacy and safety, and it is the single biological approved for AD. Currently, other mAbs are also under development for AD. In CU, mast cells releasing predominantly histamine due to only partially known eliciting causes and autoimmune components are present in many cases. The anti-IgE mAb omalizumab is very efficacious in CU resistant to antihistamines, and it is approved as 3rd step treatment.[4] Ligelizumab, a new anti-IgE mAb with a 50-fold higher affinity for IgE, and anti-IL-1β and anti-IL-5 mAbs for other forms of CU and atopic dermatitis are under investigation.[4]

Allergen-specific immunotherapy (AIT)—by administration of high doses of the causative allergens, as biologicals' products—provides symptom relief in allergic rhinitis and asthma, which can be long-lasting and show preventive effects. Other biologicals such as mAbs as add-on to AIT are expected to decrease the onset and severity of adverse events during AIT and possibly enhance efficacy. Currently, only data with omalizumab showing short-term clinical benefits are available. The lack of long-term clinical benefits questions cost-effectiveness of such interventions. Therefore, current EAACI AIT guidelines for HDM-driven allergic asthma do not recommend co-administration of biologicals with HDM AIT.[5] Large clinical trials with other biologicals are currently under development. For oral immunotherapy (OIT) in FA, anti-IgE treatment could reduce OIT-related site effects during up-dosing, allowing concomitant OIT to multiple food sources, decreasing the time to maintenance dose, and/or increasing allergen-specific thresholds in food allergic individuals without concomitant OIT.[3] Dupilumab and peanut OIT are currently the subjects of investigations (NCT03682770).

A better understanding of the molecular mechanisms underlying adverse reactions to biologicals is of outmost importance to improve diagnosis, management, and desensitization. Parenteral application of biologicals together with their intrinsic immunological activity, capacity to undergo digestion or aggregation, and immunogenicity can cause diverse adverse effects, including HSR, which significantly increased over the last years. HSRs to mAbs can be classified as type I, cytokine-release, mixed (type I/cytokine-release), and type IV reactions.[6] Diagnostic accuracy is crucial to decide the best management of HSR.[7] Diagnostic workup should

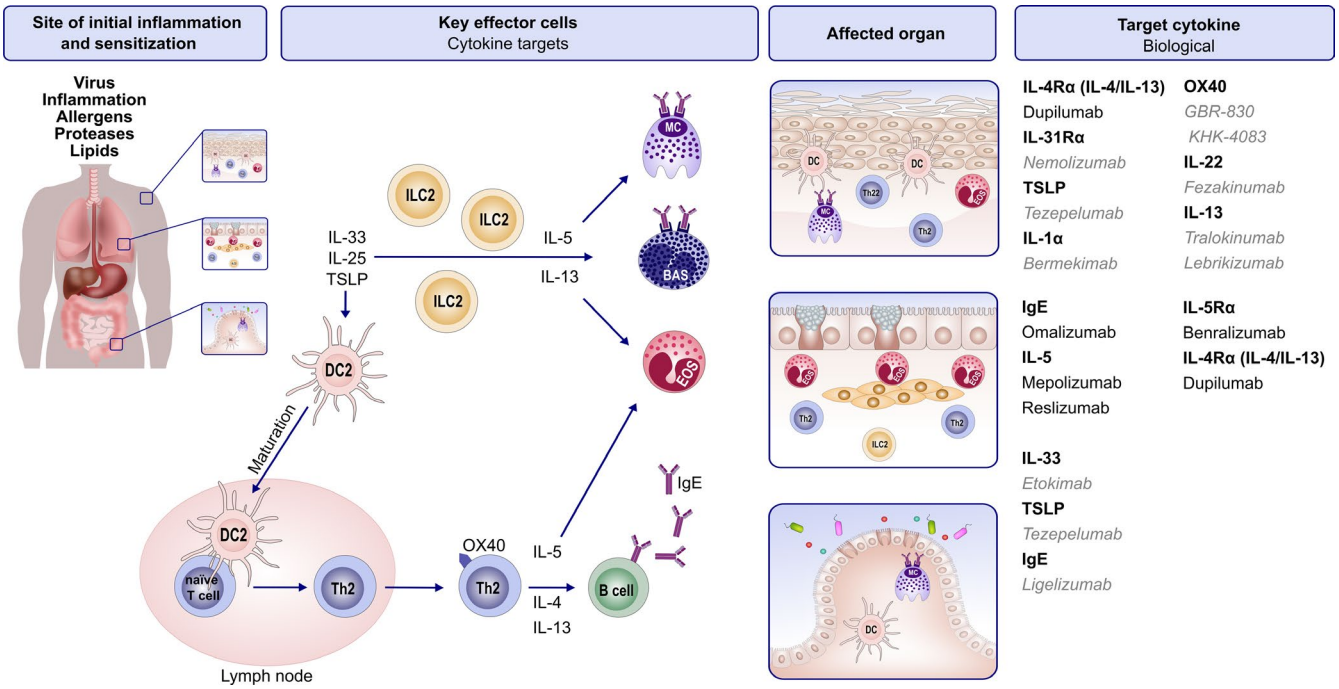

FIGURE 1 Immunological mechanisms underlying type 2-mediated allergic diseases and biologicals targeting specific pathways. Key effector cells and pathways at the different exposition sites and target organs are displayed. Approved biologicals targeting specific pathways are indicated in black. In gray and italics are shown those biologicals at different stages of development

begin with a detailed clinical history to identify the type of reaction and define risks. Skin testing requires optimization in terms of sensitivity and specificity. Nonirritating concentrations are unknown for most biologicals, and drug provocation tests with or without premedication still remain necessary.[7] The high cost of biologicals for *in vitro* tests is a relevant limitation that complicates clinical implementation. Networks of clinicians and basic researches evaluating patients with the same protocols and improving the current *in vitro* assays are needed.

The use of biologicals in pregnant women, children, and elderly deserves special considerations. AD, asthma, and FA have their peak prevalence in childhood. Clinical trials confirming safety and efficacy are needed to provide biologicals as additional treatment options in this age group. Adverse effects and underlying disease mechanisms can be age-dependent. Therefore, careful attention is required for extrapolation of data from adult studies, such as that conducted by the European Medicines Agency on mepolizumab, which have allowed drugs to be granted marketing authorization for children despite little pediatric data. Early administration of biologicals bears the chance to prevent the development of allergic diseases by interfering with the allergic march.

The number of women at reproductive age on biologicals increases, and data-based counseling on safety is required.[8] Cessation of treatment during pregnancy may affect disease control on expense of the well-being of the mother and the child. Joint efforts to report on neonatal outcomes are required. So far, only limited evidence of the safety of omalizumab is available. Case reports and series have been reported for other biologicals. Existing evidence is currently assessed via a systematic review and a position paper of the TF on biologicals in pregnancy and childhood within EAACI (Prospero CRD42018094401).

Evidence on usage of biologicals in rheumatology supports their use in the elderly based on approved indications. Although direct comparative studies have not been performed, the efficacy and safety regarding cardiovascular risk, infections, and malignancies is likely to be similar in different age groups in the adults.[9] The profile of side effects and benefit/risk balance of biologicals used on indication may favor their application over corticosteroid therapy, particularly in the elderly but additional clinical studies are demanded.

The way we understand allergic diseases and asthma has dramatically changed in the last decade in terms of complexity, dynamics, and the prospect of future risk. The endotype/biomarkers approach facilitates the transition toward precision medicine and precision health in allergic diseases and asthma. The identification and validation of novel biomarkers might well contribute to pave the way toward the clinical implementation of these concepts. EAACI Guidelines for the use of biologicals in allergic diseases and asthma, currently under development, aim to provide complete coverage of this rapid evolving field by developing recommendations in relation to all aspects of the topic (eg, surveillance, diagnosis, public health, and clinical interventions) fully based on systematic reviews of the evidence and by ensuring appropriate representation of the full range of stakeholders. Specific outcomes were defined by the Expert Panels for each of the diseases considered (asthma, CRS/wNP, AD, CU, FA, EoE) and were classified as per GRADE methodology into

TABLE 1 Biologicals in clinical use and candidates under development targeting type 2-mediated inflammation

Biological	Target molecule	Clinical indication approval	Under development
Omalizumab	IgE	Severe allergic asthma Chronic spontaneous urticaria	Food allergy Chronic rhinosinusitis with NP
Mepolizumab	IL-5	Severe eosinophilic asthma EGPA	Chronic rhinosinusitis with NP Eosinophilic esophagitis
Reslizumab	IL-5	Severe eosinophilic asthma	Chronic rhinosinusitis with NP Eosinophilic esophagitis EGPA
Benralizumab	IL-5 receptor α	Severe eosinophilic asthma	Chronic rhinosinusitis with NP Eosinophilic esophagitis EGPA
Dupilumab	IL-4 receptor α	Severe atopic dermatitis Type 2 severe asthma Chronic rhinosinusitis with NP	Chronic rhinosinusitis with NP
Tralokinumab	IL-13		Atopic dermatitis
Lebrikizumab	IL-13		Atopic dermatitis
Tezepelumab	TSLP		Severe asthma Atopic dermatitis
Etokimab	IL-33		Severe asthma, peanut allergy, atopic dermatitis and chronic rhinosinusitis with nasal polyps
Legilizumab/ QGE031	IgE		Chronic spontaneous urticaria
Nemolizumab	IL-31 receptor α		Atopic dermatitis
Fezakinumab	IL-22		Atopic dermatitis
Bermekimab	IL-1α		Atopic dermatitis
GBR-830 KHK-4083	OX40		Atopic dermatitis

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; NP, nasal polyps.

critical, important, and of low importance. EAACI Guidelines on biologicals will be of great relevance to move forward and consolidate the concept of personalized medicine and precision health for allergic diseases and asthma.

CONFLICTS OF INTEREST

Dr Chan reports nonfinancial support from Novartis and grants from Aimmune, outside the submitted work. Dr Eiwegger reports grants from DBV and Innovation fund Denmark, outside the submitted work, and he is the Co-I or scientific lead in two investigator-initiated oral immunotherapy trials supported by the Allergy and Anaphylaxis Program Sickkids. Dr Eiwegger serves as associate editor for Allergy and is in the editorial board of the IAA and the review board of JACI. Dr Gutermuth reports grants and/or personal fees from Sanofi, Novartis, Pfizer, Lilly, Abbvie, LEO, Thermo Fisher, and Janssen, outside the submitted work. Dr Jutel reports personal fees from ALK-Abello, Allergopharma, Stallergenes, Anergis, Allergy Therapeutics, Circassia, Leti, Biomay and HAL during the conduct of the study; personal fees from Astra-Zeneka, GSK, Novartis, Teva, Vectura, UCB, Takeda, Roche, Janssen, Medimmune, and Chiesi, outside the submitted work. Dr Palomares received research grants from Inmunotek SL and Novartis and fees for giving scientific lectures from Allergy Therapeutics, Amgen, AstraZeneca, Inmunotek S.L, Novartis, Sanofi-Genzyme, and Stallergenes. Dr Palomares has participated in advisory boards from Novartis and Sanofi-Genezyme. Dr Schmid-Grendelmeier reports grants and personal fees from Novartis Pharma and personal fees from F. Hoffmann-La Roche Ltd., outside the submitted work. Prof. Dr Schmidt-Weber reports grants from Novartis, grants and personal fees from Allergopharma, Leti Pharma, and Bencard during the conduct of the study. He also holds patents US2019083609 (A1) and WO2018234493 (A1) both issued. The rest of the authors have no conflict of interest in relation to this work.

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