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POINT OF VIEW

Non-allergenic immunotherapy



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The fourth session of the meeting was devoted to the new forms of immunotherapy for allergic diseases.

The understanding of the immunological processes involved in allergy has fueled the development of several innovative targeted-treatments. For many decades, in addition to allergen immunotherapy, current treatments for allergy included antihistamines, epinephrine, bronchodilators, antileukotrienes and corticosteroids have been used. All these drugs address allergic symptoms by reducing inflammation, but some of them show weak potency while others cause undesirable adverse effects. Moreover, a subset of patients experience treatment-resistant inflammation and some conditions such as food allergy have no approved therapy.

The identification of target molecules involved in the type 2 immune response and the development of monoclonal antibodies (mAb) that specifically bind those key molecules has produced major advances in the treatment of allergic diseases, such as allergic asthma and rhinitis, urticaria and atopic dermatitis. However, biologic therapy, show some drawbacks including the need of identification of the target patient population, development of convenient forms of administration and the knowledge of their safety profile. All these objectives are currently being addressed by large and expensive clinical trials.

The first biologic treatment developed for allergic diseases was omalizumab, an IgE-targeted monoclonal antibody, presently approved only for use in severe allergic asthma or chronic urticaria.¹ Currently other monoclonal antibodies directed against cytokines, such as IL-4 and IL-5 produced by Type 2 (Th2) T helper cells, eosinophils, mast

cells, innate lymphoid (ILC) cells and basophils that promote allergic inflammation are in different stages of development and/or authorization by regulatory agencies.² Responses to cytokine-directed therapies are variable, likely due to the heterogeneity of allergic conditions. However, results improve when biological therapies target specific patient populations. Thus, there is high interest in the identification the molecular phenotype of patients and conditions in order to provide a personalized medicine for allergic patients.³

The first presentation by **Dr. Marta Ferrer** from the Allergy Department of the University Clinic of Navarra, addressed the use of biological therapies for severe chronic spontaneous urticaria (CSU).⁴

Until the emergence of biologics, uncontrolled cases of CSU, despite the regular use of high doses of antihistamines and corticosteroids, were treated with cyclosporine showing undesirable side effects.⁵

Rituximab, Quilizumab, Ligelizumab, and TNF-alpha inhibitors showed opposite results in different studies, but Omalizumab has demonstrated to be effective in autoimmune and non-autoimmune CSU with very good results and a significant improvement of the Urticaria Activity Score 7 (UAS7).^{6,7}

The exact mechanism is not well-known. Dr. M. Ferrer suggested that Omalizumab may not only bind to circulating IgE, but also to remove bound IgE from its receptor, which results in an inhibition of mediator's release.

Dr. M. Ferrer gave details of the results obtained in the three clinical studies in which she actively participated. The most effective dosage, faster in controlling symptoms, is 300 milligrams. The global effect of omalizumab increases with time and that the clinical response is maintained.

However, she pointed out some unmet needs: (a) identification of predictive biomarkers for responders, (b) definition of the best administration protocol, (c) to investigate the

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exact mechanism of action (in order to design new biologicals not only to control the disease but to definitively cure the condition).

The second presentation, by **Dr. Santiago Quirce** from the Allergy Department of Hospital La Paz, addressed the use of new biological agents as new therapies in severe uncontrolled asthma.⁸

Several pathophysiological mechanisms are involved in the development of asthma. In order to prescribe the most appropriate therapy, it is necessary to identify the key processes participating in each case.⁹ An endotype driven approach guided by biomarkers such as blood or sputum eosinophilia or serum periostin seems to predict treatment response.¹⁰

In asthma, the type 2 immune response endotype has been related to response to inhaled corticosteroids. However, the administration of corticosteroids needs to be prolonged or lifelong and not always achieves control of disease nor prevents exacerbations. Many targeted biological therapies are in various stages of clinical development for patients with type 2 immune response-driven inflammation: anti-IL-4/IL-13, anti-IL-4, anti-IL-5, and anti-IgE antibodies, as well as CRTH2 antagonists.¹¹

Omalizumab is the only anti-IgE mAb approved for the treatment of severe allergic asthma. It has proven efficacy in terms of asthma control, use of rescue and controller medication, decrease in exacerbations and improvement of quality of life. However, it remains as an add-on therapy providing no persistent cure of asthma. New human anti-IgE mAb, provide some advantages, higher IgE affinity (ligelizumab) or binding to IgE already bound to low-affinity receptors (8D6).

The presentation moved on to the two anti-IL-5 mAb developed in order to achieve a reduction in blood and tissue eosinophils. Several clinical trials (DREAM, MENSA, DREAM & MENSA, SIRIUS, COSMOS, ..., etc.) have shown that Mepolizumab and Reslizumab reduce exacerbations and improve asthma control, and Benralizumab, an anti-IL-5R α , reduces eosinophil counts and improve asthma symptoms.

Other mAbs as Lebrikizumab, an anti-IL-13 mAb, showing effectiveness in patients with Th2-high phenotype; Dupilumab, an anti-IL-4 mAb probably useful in all asthmatic patients, and Brodalumab an anti-IL-17 mAb seems to be effective in patients with high bronchodilator reversibility, but still early to know the significance.¹²

The presentation concluded underlining the need for more selective and clinically effective targeted therapies for uncontrolled severe asthma patients as well as the need for more experience in daily clinical practice. The unpredictable risks and the economic burden of the new anti-asthma therapies may be prevented by the development of a set of reliable biomarkers to identify the ideal target patient population.

The third speaker was **Dr. María Escribese** from the Medical Sciences Department of the Faculty of Medicine, CEU San Pablo University of Madrid, who presented some findings concerning cancer immunotherapy, which may play a role in allergic diseases.¹³

The disruption of the immune system homeostasis induces the progression of diseases via the "immunoedition", which favors evasion of the immune

system.¹⁴ The new strategies in cancer therapy aim to redirect the immune response toward the recognition of tumor antigens and activation of effector CD8 T cells, NK cells and macrophages to eliminate the tumor.

In cancer, immunotherapy is approached by two different forms: passive or active. Passive immunotherapy is addressed in order to compensate an immunological deficiency, while active immunotherapy aims to stimulate effector functions by inhibiting immunological checkpoints. This is achieved by the use of mAbs to promote the initial and effector phases of T cells in their response to tumor antigens. Nowadays, this is the most promising treatment in cancer.¹⁵

The last part of the presentation was devoted to some lessons from cancer immunotherapy which may apply to allergy. Costimulatory molecules as CTLA-4, which is an inhibitory molecule that enforces an activation threshold and attenuates proliferation of tumor-specific T lymphocytes. CTLA-4 molecules are present on the regulatory T-cells (Treg) and are involved in the induction of oral tolerance and suppression of food allergy.¹⁶

Dr. M. Escribese concluded that cancer immunotherapy opens new lines of research into other immunological diseases such as allergy. The induction of a regulatory response is necessary to avoid allergic progression. In fact, nowadays, this is the main mechanism attributed to allergen-specific immunotherapy.

The discussion was opened by Dr. L. Prieto, who asked for the role of eosinophils on the airways and the need of eosinophil markers. Dr. S. Quirce stated that peripheral eosinophilia quantification is a better marker than sputum or lung tissue (by biopsy) eosinophil count. In this issue, there is a change in the expert's opinion and no one knows the exact role of eosinophils and other biomarkers in the indication of the various anti-asthma biologicals.

Dr. L. Prieto asked about the relation between peripheral blood autoimmune events (antibodies against mast cells receptors) and the active relationship between IgE and its receptor. Dr. M. Ferrer explained some findings concerning the use of omalizumab on autoimmune CSU. Patients with a positive clinical response were able to activate basophils with their own serum suggesting there is an autoimmune background. Probably new mechanisms will explain the effect of omalizumab in CSU.

Conclusions

The last session, included three reports of interesting new approaches for the treatment of allergy diseases. Dr. M. Ferrer pointed that adult patients suffering from chronic spontaneous urticaria not responding to conventional therapy with antihistamines and/or corticosteroids may benefit from Omalizumab therapy. Dr. S. Quirce proposed targeting concrete phenotypes of asthma by the use of specific monoclonal antibodies and Dr. M. Escribese described the types of immunotherapy used in cancer, and their possible roles in allergy diseases.

Taken together, research in the field of allergic diseases continues to be promising. Indeed, several new therapeutic approaches to different allergic conditions have also

been reported. In spite of this progress, the role of allergen non-specific immunotherapy remains a subject for further research.

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