Original Article

Translational Allergy and Omalizumab: The Pioneer

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ABSTRACT

Backgound: The introduction of monoclonal antibodies into therapy has brought great progress in every field of medicine. Omalizumab is the first monoclonal antibody successfully used in allergology. We wanted to evaluate the impact in the medical literature of this molecule. **Materials and Methods:** We have identified omalizumab as the reference molecule in clinical allergology to evaluate the impact of the translational approach in this field throw the amount of data present in the literature on this subject. We have therefore carried out a research on the three main scientific databases (PubMed, Scopus and WoS) and we have documented the growing number of scientific publications on this molecule in over 20 years (1996 first publication retrived for omalizumab) and since 2003 when the molecule received the authorization by the Food and Drug Administration. **Results:** More than 5,000 scientific articles have been published with a maximum of almost 500 per year in 2018, which will certainly be exceeded in 2019 based on data to date. Since it is the first biologic drug approved for the treatment of immuno-allergic disorders with consolidated results in the treatment of asthma and chronic urticaria, while it is widening its therapeutic potential, we have chosen omalizumab as an example of the possibilities and successes that translational research can also reach in allergology. **Conclusion:** Such a significant impact of this molecule in the medical literature goes hand in hand with the leading role that this molecule has today in the therapy of allergic diseases. The impact of omalizumab in a field such as allergology in which progress is still rather slow demonstrates how, even in this discipline, understanding the finer pathogenetic mechanisms allows to develop targeted therapy with great benefits.

Key words: Allergy, IgE, Atopy, Omalizumab, Asthma, Atopic dermatitis, Translational allergy, Translational medicine.

INTRODUCTION

Translation in allergy

The vast horizon of translational medicine has been opened by the impact of the enormous technological and scientific advances of these recent years. It represents the medicine which, breaking the rules, wants to bring the ideas, suggestions and discoveries that hatch in the "closed" laboratories to the patient's bed, to personal care, to improve disease prevention, diagnosis and treatment. It wants effectively and immediately transfer the innovation and dynamism of the experimenter to the certainty of the care and relief of the person. In other words transforming research into improved health without waste of resources and in shortened times.[1]

Basic science can no longer represent a world in itself, sometimes a little sterile, lacking a concrete and beneficial purpose, but it must be combined and find its main objective in putting itself at the service of the end user: the patient. It moves from the laboratory, from cell cultures, from animal models[2] to humans. There must be a communion of objectives and intentions, a continuity of thought and organization, a sort of passage from hand to hand and mind to mind that from the bench reaches the hospital ward. This process, this transfer, takes place through various passages from the basic

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inquiry into pathophysiology, to the identification of potentially targetable pathways, up to the development of new drugs. Each of these steps is a fundamental step in which one can effectively find a practical implication applicable to the preventive-diagnostic-therapeutic pathway.

Too often in the past, Science has developed on an individualistic model, of independent experts, little inclined to sharing, cooperation and communication. Doing translational medicine instead means being a community, being a force all together, it means finding a common language and a common purpose. The translational approach cannot disregard the close interaction of individuals with different skills to make available for a common purpose. Communication, information exchange, teamwork also promote feedback between clinicians and basic scientists, so that research is truly a two-way process from the clinic to the laboratory and vice versa. Each actor must convey knowledge, sensibilities, ideas for a common "making".

Among subspecialties of medicine, allergology probably entered this process with some slowness and delay but now it is fully entitled to several successfully achieved goals. Today, allergology is a very dynamic area in translational research with very promising developments, able to make the results of basic research applicable to clinical use. Several targets successfully translated into practice and some others are rapidly progressing towards clinically effective results. As tumor necrosis factor alpha inhibitors changed the life of many people affected by several reumathic diseases,[3] the introduction of biological therapies in allergology changed dramatically the therapeutic approach and the quality of life of people suffering from allergic disorders.

Mechanisms that initiate and maintain the allergic reaction have been substantially elucidated in recent years, while to develop personalized medicine efforts have been made to distinguish patients suffering from allergic disorders.[4]

Good knowledge of immunological mechanisms driving allergy development and allergen tolerance is fundamental to implement a systematic strategy for drug design targeting specific molecules involved in these processes.[1]

Furthermore, to develop individual therapies it is necessary to identify biomarkers that objectively and accurately examine pathophyisiological processes and sensitivity to therapeutic intervention. To further elucidate these mechanisms, an invaluable data resource come from the feedback of preclinical work and clinical trial results.

In the treatment of allergic diseases a wide range of biologic drug candidates that can be broadly grouped into two distinct groups: a) biologics targeting soluble and membrane-bound IgE and b) biologics targeting cytokines and cytokine receptors. Both have been developed thanks to the advances in the field of therapeutic antibodies. The role of IgE in allergy was known for a long time and the idea of acting on them to block allergy attracted the interest of researchers. The revolutionary introduction in human therapy of monoclonal antibodies found in IgE its first successful target and the IgE signaling transduction pathway is one of the most investigated for the development of new drugs due to their key role in the activation of allergic cascade. Allergy affects about 25% of the population, represent the most fast growing and widespread chronic disease and will become more frequent as people became older.[5] Glucocorticoids with their numerous side effects and antihistamines have always been the cornerstone of the treatment of allergic diseases and the need for new molecules was strong.[6] Monoclonal antibodies (mAbs) have high specificity and affinity for the target and being degraded to aminoacids do not give rise to toxic metabolites thus they offer numerous advantages compared to conventional drugs and in the last decade, the use of mAbs has expanded exponentially. They are relatively stable with an elimination half-life from weeks to months. The basic structure of Immunoglobulins G (IgG) is common to all mAbs used in human therapy: a high molecular weight heterodimeric protein made of four chains two with identical light polypeptide chains and two with identical heavy chains. At the beginning murine Abs entered therapy but having high immunogenicity their use was limited and thanks to recombinant DNA techniques were replaced by chimeric antibodies (Abs) first, than by humanized Abs and finally by human mAbs. Currently for the treatment of allergic diseases, all antibodies are humanized or fully human IgG antibodies.

Omalizumab and other biologics

Omalizumab is the first therapeutic monoclonal antibody of allergological interest that has landed at the patient's bed from the bench.[7] The Food and Drug Administration (FDA) approved omalizumab in 2003 and the European Medicinal Agency (EMA) in 2005. In the European Union, omalizumab is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple

documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled Beta2-agonists and as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment.[8] Omalizumab is an immunoglobulin E specific IgG1 k antibody (recombinant DNA-derived humanized monoclonal antibody) that targets circulating free IgE and rapidly attenuates their serum levels, hence reducing their interaction with FCεRI receptors and with CD23 (FcεRII). Furthermore, it down regulate these receptors on mast cells and basophils, reducing the cellular responses to allergens and seems to induce B-cell anergy thereby decreasing IgE synthesis.[9] The clinical use of this molecule has a rather long history and has been a pioneer for many new molecules that have been authorized by competent authorities and others that are still under evaluation.[10] Over these years it has also been studied as an off-label treatment for numerous allergic conditions,[11] including allergic rhinitis, food allergy,[12,13] atopic dermatitis[14] and other inflammatory skin conditions,[15,16] physical urticarias,[17-20] eosinophilic gastrointestinal disease, idiopathic anaphylaxis, mastocytosis and allergic bronchopulmonary aspergillosis.[21]

Our search

Literature search is the task of finding relevant information from literature, a fundamental step in biomedical science from basic research to clinical sciences to make important clinical decisions.[22,23] Several search engine for biomedical literature are accessed each day worldwide.[24] PubMed is one of the most widely used search engine built and maintained by the United States National Center for Biotechnology Information at the US National Library of Medicine.[25] Scopus is the largest abstract and citation database of peer-reviewed literature by Elsevier. Web of Science (WOS) is a platform to access research literature by Clarivate Analytics. In this review, we searched the PubMed, Scopus and WoS electronic database individually using keyword "omalizumab" with no filters in all fields.

RESULTS

Results in Table 1 show: on PubMed retrivied date 2001-2019, on scopus retrivied date 1996-2019; on WoS retrivied date 2001-2019.

DISCUSSION

Since 1996 the number of publications on omalizumab is progressively increasing, reaching the maximum on all three research sources in 2018 and presumably based on this year's partial data, these results will be exceeded.[26,27] This is to demonstrate the value of the molecule that in over twenty years has achieved excellent results and continues to expand its role in the treatment of immuno-allergic pathology.[28] It therefore represents a paradigm that confirms the growth and the value of translational research in allergy. Currently several molecules are approved for the treatment of allergic diseases or are under study (Table 2). Mepolizumab and reslizumab that bind directly to interleukin (IL)-5 and prevent its link with IL-5 receptor (IL-5R),[29] benralizumab that binds to the α subunit of IL-5R on eosinophils and basophils, thus preventing IL-5 binding and amplifying the ADCC function of these cells by activating natural killer cells to perform apoptosis and dupilumab that has been specifically designed to inhibit signaling of IL-4 and IL-13 are the mAbs currently approved for the treatment of severe asthma other than omalizumab. Since 2003, when the Food and Drug Administration (FDA) approved omalizumab, a number of new biologics have entered clinical development, directed against various inflammatory targets (anti-CD4, anti-CD25, anti-OX40L, anti-interleukin (IL)-4, anti-IL-13, anti-IL-5, anti-IL-33, anti-IL-17 and anti-IL-25), but to date only one has been used as a long-term treatment in clinical practice. Three biological agents are currently available in clinical practice specifically indicated for the treatment of severe asthma:[30,31] the anti-IgE omalizumab and the anti-IL-5 mAbs mepolizumab and reslizumab. Recently

Table 1: "Omalizumab" Search results on PubMed, Scopus and WoS on 14/12/2019.

	PUBMED	SCOPUS	WOS
Total	2387	5781	3954
Article	1958	2391	1408
Review	762	2147	656
Letter	281	317	364
Editorial	63	259	181
Note		216	
Meeting abstract			1286
Proceedings paper /conference paper		200	52
Book chapter	12	48	21
Correction/erratum		25	24
Bibliography			1
Comment	110		
New item/ early access/ article in press		11	11
Short survey		170	

Table 2: Biologicals approved or under development for the treatment of allergic diseases.

Biologic	Target
Omalizumab	IgE
Ligelizumab	IgE
Quilizumab	IgE
MEDI4212	IgE
Dupilumab	IL-4Rα
Pitrakinra	IL-4Rα
Mepolizumab	IL-5
Reslizumab	IL-5
Benralizumab	IL-5Rα
Enokizumab	IL-9
Lebrikizumab	IL-13
QBX258	IL-4/IL-13
BMS-981164	IL-31
Nemolizumab	IL-31
Tezepelumab	TSLP
Tralokinumab	IL-13
Fevipiprant	CRTh2 (PGD2-r)
Etokimab	IL-33
MEDI3506	IL-33
RG 6149/AMG 282	IL-33R (ST2)

other than MoAbs and mutated molecules (Pitrakinra), several selective, orally active, DP_2 receptor antagonists and a selective DP_1 receptor antagonist (Asapiprant) have been investigated and represent an emerging therapeutic class due to the pathophysiological role of prostaglandin D_2 (PGD_2) in immuno-allergic inflammation, although not biological agents.[32]

CONCLUSION

Allergies are a fast growing health problem worldwide whose therapeutic approach remained unchanged for decades.[33] Humanized MoAbs targeting IgE, cytokines, cytokines receptors and other molecules involved in the allergic reaction show great promise. It is the result of the incredible progress of translational research in the last few years in allergology, thanks to the development of specific studies aimed at drug development and testing in new infrastructures and with novel technologies.[34] Translational allergology must take courage from these results and implement its efforts and its speed on this promising road. We urgently need the safe development of new effective molecules in the diagnosis and treatment of allergic disorders and the application of newer technologies in the clinics.[35,36] The complex human setting need caution to translate basic studies and it is necessary a collective effort to bring close together clinical and basic scientists in a joint endeavour to make the bench to bed round trip fruitful and useful.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

mAbs: Monoclonal antibodies; **IgG:** Immunoglobulins G; **Abs:** Antibodies; **FDA:** Food and Drug Administration; **EMA:** Euorpean Medicinal Agency; **FCεRI:** High affinity IgE receptor; **WOS:** Web of science; **IL-4:** interleukin 4; **IL-5:** Interleukin-5; **IL-13:** Interleukin-13; **IL-17:** Interleukin-17; **IL-25:** Interleukin-25; **IL-33:** Interleukin-33; **ADCC:** Antibody-dependent cellular cytotoxicity; **PGD2:** Prostaglandin G2; **DP1:** Prostaglandin 2 receptor 1; **DP2:** Prostaglandin 2 receptor 2.

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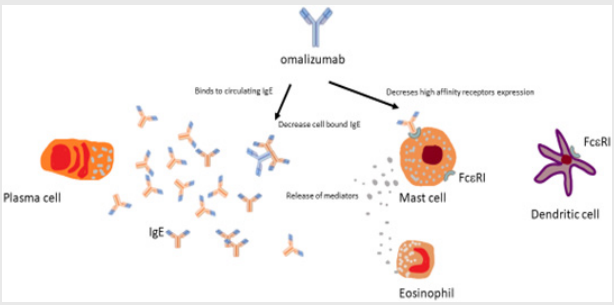
PICTORIAL ABSTRACT



Mechanism of action of omalizumab. It binds to IgE preventing and reducing its interactions with eosinophils, mast cells, basophils and dendritic cells; decrease the expression of the high affinity IgE receptor. These effects reduce allergic inflammation and symptoms.

SUMMARY

Allergies are rapidly increasing in last decades and represent the most common immunological diseases. The mechanism of disorders such as asthma, rhinocongiuntivitis, urticaria, atopic dermatitis, food and drug allergies and anaphylaxis still remain unclear and consequently treatments is mostly still symptomatic and aspecific. Developments of new therapies are limited. Omalizumab is a monoclonal antibody used in the treatment of allergic diseases such as asthma and chronic urticaria. it is the first authorized monoclonal antibody in allergy. After 20 years he confirms his leding role in the clinic and consequently in the medical literature. After all these years the spectrum of diseases in which this molecule is effective is still growing. It represents a point of reference in the therapy of allergies and must be a stimulus for the development in this discipline of equally effective new molecules. Allergology despite the progress of recent years still has as its therapeutic basis the use of few drugs with modest efficacy. The development of effective targeted drugs tailored to the needs of patients is a stronger requirement also in allergology.

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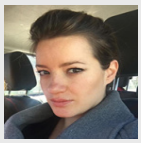

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