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Use of omalizumab in women Mexican patients diagnosed with moderate to severe non-atopic asthma: an observational real-life study in a university hospital

Abstract

Introduction: While up to 50% of patients with moderate to severe asthma have no evidence of allergy, IgE has been linked to asthma regardless of atopic status. It has already been described that omalizumab, an anti-IgE monoclonal antibody, significantly benefits a subset of patients with non-atopic asthma.

Methods: 19 female Adult patients who, despite daily treatment with or without maintenance oral corticosteroids, had uncontrolled moderate to severe non-atopic asthma, were assigned to receive omalizumab at doses of IgE levels. The primary endpoint was the change in the clinical and functional parameters of the patients by means of asthma control examination.

Results: After 52 weeks of administration of Omalizumab they showed a moderate increase in FEV1, clinical and functional parameters. The symptomatic improvement of the patients was mainly due to an ACT increase of 10 to 20 points. Good tolerance to the drug was also observed, without any serious adverse effects and improvement in the quality of life of the patients.

Conclusions: Omalizumab has a therapeutic role in moderate to severe non-atopic asthma. Our results support the clinical efficacy of omalizumab in women non-atopic asthmatic patients.

Keywords: non-atopic asthma, omalizumab, quality of life

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Herrera-García José Carlos,[1] Arellano Montellano Ek Ixel,[1] Jaramillo Arellano Luis Enrique,[2] Espinosa Arellano Andrea[2]
[1]Department of Pulmonology-Asthma Clinic and COPD, University Hospital of Puebla, Mexico
[2]Department of Undergraduate-Benemérita Autonomous, University of the State of Puebla, Mexico

Correspondence: José Carlos Herrera García, Department of Pulmonology-Asthma Clinic and COPD, University Hospital of Puebla, 25 poniente 1301 Col. Volcanes, CP 72410, Mexico, Email jchg10@yahoo.com.mx

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Introduction

Bronchial hyperreactivity, reversible limitation to airflow and recurrent episodes of wheezing, breathing difficulties and cough are the disorders that define asthma, a chronic inflammatory disease of the airways. However, it is now accepted that asthma is, in fact, a complex syndrome with different clinical and inflammatory phenotypes. In the last decades, there were two major changes that greatly modified the treatment and evolution of asthmatic patients. First, international regulations recommended, in 1992, the use of inhaled corticosteroids (IC) as first-line anti-asthmatic therapy for subjects with persistent asthma. In the following years, numerous studies were carried out in order to identify the optimal dose of IC for each category of severity of asthma. In parallel, other drugs were introduced, for example, leukotriene modifiers and long-acting beta agonists, and important advances were made in immunotherapy strategies.[1–3]

At the beginning of 2000, biological antiasthmatic therapies emerged, that is, agents designed to modify the action of different proteins or molecules involved in the inflammatory marry that characterizes asthma. Monoclonal antibodies are a form of immunotherapy, in which preformed antibodies against a specific antigen are injected into the body. Due to its high specificity, monoclonal antibodies can act on cellular or circulating antigens and thus suppress the function of cytokines, immunoglobulins, hormones or proteins responsible for unwanted biological effects. Omalizumab: the first monoclonal antibody for the treatment of asthma. Omalizumab is a humanized monoclonal antibody of murine origin that recognizes the Cε3 domain of human IgE, the portion that participates in the binding of immunoglobulin to FcεRI in mast cells and basophils. However, omalizumab binds to free IgE and not to IgE bound to FcεRI.[4]

The administration of omalizumab is associated with a rapid reduction in serum IgE levels (of around 99% within 2 hours after treatment) and with a lower expression of FcεRI in basophils, dendritic cells and monocytes. After 3 months of treatment, the expression of FcεRI in basophils is reduced by up to 93%. The lower expression of FcεRI in the dendritic cells would decrease the processing and presentation of the allergens. Omalizumab decreases the eosinophil count in peripheral blood, tissues and sputum. The original approval for omalizumab was not substantially modified; The drug is indicated as adjuvant therapy in patients with moderate or severe allergic asthma who do not respond favorably to conventional treatment. Although most studies were performed in patients with asthma not controlled with IC, omalizumab was essentially approved for use in patients with asthma dependent on oral corticosteroids. Currently, the drug is used in patients with serum IgE levels of 30 to 1500IU/ml (and not 30 to 700IU/ml as previously considered).[5–7]

The continuity of the therapy, once the patient has responded, is still a matter of debate. In one study, the asthmatic symptoms reappeared when the treatment was interrupted. According to the new theory that considers omalizumab could improve the course of the disease, today treatments are usually maintained for several years; possibly in these cases, the dose may be reduced. According to the results of a mathematical model, the synthesis of IgE would reach a new equilibrium, around 5 years after the beginning of treatment with

omalizumab. In this context, therapy should be maintained for that period approximately.[8]

It is necessary to remember that the effects of omalizumab are progressive and that the interval until the response appears is not uniform; According to the results of a study that analyzed, in particular, the levels of free IgE, treatment could be interrupted before 5 years in some patients, while, in other patients, it may never be suspended. Although the effects of corticosteroids are not specific, the information as a whole supports a more important modulation of inflammation mediated by Th2 lymphocytes, characterized by high levels of nitric oxide in exhaled air, eosinophilia in sputum and increased levels of the levels of periostin in the airways. According to the most recent studies, the latter seems to be a particularly important marker of allergic inflammation and, especially, of tissue eosinophilia. In a study in patients with severe, uncontrolled and persistent asthma, the rate of acute exacerbations was reduced by 30% in patients with high serum levels of periostin, compared to 3% in patients with low levels, after treatment with omalizumab.[9]

Omalizumab in non-atopic patients

Not all patients with asthma present the specific indicators of atopy (positive skin tests or specific IgE for allergens in serum and high levels of total IgE). Localized allergic disease has been recognized long ago in a group of patients with rhinitis, presumably not atopic. In these patients, allergen-specific IgE was detected in nasal secretions, a situation that led to the introduction of the concept of entopia, that is, the localized response in the mucosa, independently of the systemic atopic expression. In opinion of researchers they emphasize that the possibility seems to be valid also for some patients with skin, gastrointestinal, ocular and upper respiratory tract disorders. In this context, the distinction that has been made over the years between allergic asthma and "non-allergic" asthma is increasingly being discussed. In the latter case, IgE would also have a fundamental physiopathological role. In fact, in the bronchial biopsies of patients with "non-atopic" asthma, cytokines corresponding to a Th2 collaborative pattern were also found; therefore, in both types of asthma, the similarities are more numerous than the differences. The estimated prevalence of nasal polyposis is 2% to 4%; The expression of cationic protein of eosinophils, IL-5 and IgE is important in the tissue of nasal polyps. In a study in patients with nasal polyposis and asthma, treatment with omalizumab was effective, even in non-allergic subjects.[10–15]

Possible mechanisms of action

Numerous studies revealed multiple similarities between allergic and nonallergic asthma; Asthma associated with high local, but not systemic, levels of IgE has long been called intrinsic asthma. However, at least two papers revealed that IgE can be synthesized by T lymphocytes in non-allergic patients. This IgE binds to high affinity receptors and triggers the same reactions that occur in allergic patients. The fact that IgE can be synthesized exclusively at the local level supports the use of omalizumab, also in patients with asthma presumably not allergic. The findings together show that omalizumab decreases the expression of FcεRI in basophils and in plasmacytoid dendritic cells, as occurs in individuals with allergic asthma.[16]

Three possible mechanisms have been proposed to explain the favorable response to omalizumab in patients with "non-allergic" asthma.

I. The first one has to do with the possible "local allergy", characterized by the presence of allergen-specific IgE only in the airways.

II. Second, one group demonstrated that the binding of IgE to FcεRI activates intracellular signaling pathways that culminate with the production of IL-4, IL-6, IL-13 and tumor necrosis factor alpha, among other cytokines , associated with greater survival of the mast cells, in the absence of the cross-linking of the receptors on the cell surface, induced by the union of these with the specific allergens.

III. Third, it is possible that omalizumab modulates the responses of innate immunity. Plasmacytoid dendritic cells, involved in allergic responses, also play an essential role in the responses of innate immunity against infections, especially viruses. The dendritic cells of patients with asthma strongly express FcεRI, and, therefore, participate in innate and adaptive immunity. Omalizumab, by modulating the expression of these receptors, would favor responses against viruses and, thus, reduce the risk of exacerbations, in relation to viral infections.[17–26]

Clinic tests

Although clinical trials are still scarce, some studies showed a favorable evolution in patients with non-atopic asthma, treated with omalizumab, especially in subjects with severe asthma, dependent on corticosteroids.

General purpose

To determine the clinical improvement in patients diagnosed with Moderate to Severe Non-Atopic Asthma. The data available to date suggest that treatment with omalizumab may be useful in certain patients with non-allergic asthma. There are already different works that support the use of omalizumab in Non-Atopic patients.

Specific objectives

a. To describe the clinical improvement of Omalizumab in moderate to severe asthma patients with Omalizumab.

b. To determine the degree of functional improvement by means of spirometric records after the use of omalizumab.

c. Describe the improvement by ACT (Asthma Control test) after the administration of Omalizumab.

d. Describe the clinical characteristics of patients with clinical improvement after Omalizumab administration.

The determination of the improvement of non-atopic asthma patients is a finding that is determined in works already described of their efficacy and safety in the administration to uncontrolled patients, this observational and real-life work in Mexican patients in a cohort in the consultation of Pneumology of the University Hospital of Puebla will help us to initiate treatment under real evidence the efficacy of treatment in uncontrolled patients.

Material and methods

Prospective Observational Real Life Study carried out in the Department of Pulmonology at the Asthma/COPD Clinic at the University Hospital of Puebla in the period from January 1, 2017 to January 1, 2018.

Under the following Inclusion Criteria:

Criteria for the inclusion of participants

i. Women over 18 years of age.

ii. Moderate / severe non-atopic asthma defined by the GINA / ATS / BTS and GEMA 2017 guidelines.

iii. Diurnal and nocturnal symptoms at least 3 days / week in the last 3 months prior to the screening visit (despite taking inhaled corticosteroids with or without long-acting β2-agonists or leukotriene blockers)

iv. Forced expiratory volume prebronchodilator in 1 second (FEV1) 40-80% predicted; reversibility of ≥12% in FEV1 in response to inhaled β□ agonist documented at any time within the last 2 years

v. Negative in vitro IgE tests determined by Allergology services of the University Hospital.

Criteria for the exclusion of participants

I. Smoking during the previous year or smoking history and man

II. Women who are pregnant or nursing or at risk of pregnancy

III. Treatment with maximum doses of inhaled steroid or equivalent in control.

IV. Hospitalization for asthma or exacerbation that requires systemic therapy with corticosteroids within 3 months after the screening visit.

V. History of potentially fatal asthma, defined as an episode of asthma that required intubations and / or was associated with hypercapnia, respiratory arrest and / or hypoxic seizures

VI. Patients in whom, in the opinion of the study investigators, omalizumab therapy would normally require caution (history of autoimmune disease, renal or hepatic failure, hyperimmunoglobulin E syndrome, allergic bronchopulmonary aspergillosis, and diabetes mellitus).

Mainly describes the patients who attend the outpatient clinic. The study was evaluated and approved by the Hospital Science and Bioethics Committee.

Development: Once the diagnosis of moderate or severe non-atopic asthma was confirmed, the patient had post-bronchodilator spirometry, blood biometry, D-Dimer, and chest X-ray. A previous ACT questionnaire was performed, Omalizumab treatment was indicated by IgE levels and ACT was again performed after the application of Omalizumab 2 weeks later, each record every 2 weeks. At the conclusion of the data, they were entered into a database to determine the follow-up. The presence of exacerbation of any kind (mild, moderate to severe) was documented, considering the severity of it was entered to be documented, as well as adverse effects to the application.

Results and discussion

We present 19 female patients diagnosed with moderate to severe non-atopic asthma who presented negative skin tests, IgE level between 190 and 30 IU/ml. 75% have representative eosinophilia (greater than 2% or greater than 200 total cells). More than 1 exacerbation during the protocol which only needed symptomatic as antihistamines or extra doses of beta adrenergic. 75% were using oral steroids and 75% suspended them at the end of 52 weeks. The dose of Omalizumab fluctuated between 2 and 3 vials every 15 days as marked by the previous work, which mentioned as standard dose 2 vials every 15 days. Most of the adverse reactions were mild and those previously reported without cases of anaphylaxis. 75% improved their ACT from 10 to 20 points and 25% improved their ACT from 10 to 25 points, something that has been reported in patients (Table 1).

Table 1 We included 20 patients with Moderate to Severe Non-Atopic Asthma Diagnosis with the following characteristics

Characteristic	Results
Number of patients	N = 20
Average age	25±10
Sex	19 women (100%)
Negative skin tests	-100%
IgE level	110±80
FEV1/FVC ratio	66.2±8
FEV1 (%)	65.3±8
Response to Bronchodilator (%)	15±3
Number of eosinophils	
≥ 2% or more than 200 total cells	15 (75%)
≤ 2% or less than 200 total cells	5 (25%)
BMI	27±3
Scale Borg	5±1
Leukocytes (µg/dl)	5000±2500
Exacerbations	1.5±0.5
Use of inhaled corticosteroids	19 (95%)
Use of oral corticosteroids	15 (75%)
D Dimer (UI/L)	125±80
Dosage of Omalizumab	300±150
Adverse reactions	
Pain in the puncture site	15 (75%)
Edema at the puncture site	3 (15%)
Pharyngitis	3 (15%)
Flu-like syndrome	1 (5%)
Anaphylaxis	0 (0%)
Symptomatic improvement	
ACT preomalizumab (points)	20 (100%) 10 points
ACT postomalizumab	15 (75%) 20 points 5 (25%) 25 points
They suspended oral steroids	15 (75%)

Conclusion

This work demonstrates in a Mexican population of patients diagnosed with Moderate to Severe Asthma. Non-atopic use of omalizumab substantially improves symptoms, quality of life and decrease in exacerbations. The effectiveness and safety of the drug is

demonstrated in a real life study. in patients- The use of omalizumab in patients with non-atopic asthma is an effective option to date in a few Mexican women cohort and is equal than another countries.

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Conflict of interest

Author declares there is no conflict of interest in publishing the article.

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