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# Use of Omalizumab as Treatment in Patients with Moderate and Severe Non-Atopic Asthma and Associated with Asthma-COPD Overlap Syndrome (ACOS)

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## Abstract

The asthma syndrome has many manifestations, termed phenotypes that arise by specific cellular and molecular mechanisms termed endotypes. Understanding helps clinicians make rational therapeutic decisions. Omalizumab has been widely used in clinical practice in Europe and America for over a decade as an add-on therapy to treat patients who have severe asthma. These real-world clinical effectiveness studies have confirmed the benefits, cost-effectiveness, and clinical utility. The purpose of this review is to present the effects of anti-IgE treatment in severe non-atopic asthma and in asthma-COPD overlap syndrome (ACOS). This study describes that the use of omalizumab therapy reduces IgE expression and IgE sensitization of target cells within the bronchial mucosa while exerting a favorable effect on lung function in the short term, as assessed by changes in forced expiratory volume in 1 s (FEV1).

**Keywords:** omalizumab, non-atopic asthma, ACOS, phenotypes, severe asthma

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## 1. Introduction

Severe asthma is a highly heterogeneous and burdensome disease that requires individualized assessment and management. The exact prevalence of severe asthma is unknown, but it has been reported to affect 5–10% of the population with asthma. Although some patients have

Atopic Patient	Non-Atopic Patient
With o without Eosinophilia	With or Without Eosinofilia
Skin prick test positive	Skin prick test negative
IgE > 150 U/L	IgE < 30 U/L
	30-150 U/L
	or > 150 U/L

Figure 1. Definitions.

asthma that remain poorly controlled despite high doses of inhaled corticosteroid (ICS) with or without additional controlled therapies including long-acting muscarinic antagonists and theophylline. Uncontrolled severe asthma significantly affects the activities of daily living, morbidity, mortality, quality of life (QOL), and health care use. Indeed, severe asthma accounts for approximately 50% of all asthma-related health care costs, direct (physician visits, hospitalizations, intensive care, and medications) and indirect (missed school days and work absenteeism). Categorically, uncontrolled and severe asthma remains a health and economic burden in many countries. Nowadays, we have a targeted therapy to control the burden disease with excellent results. In this chapter, we discuss the benefits of the use of omalizumab (OmAb) in patients with non-atopic and asthma COPD overlap syndrome (ACOS) phenotype. [1] (Figure 1).

2. Non-atopic asthma and IgE

The concept of asthma in our practice is a complex disease. Atopy is a familiar knowledge but the significance of non-atopic or non-allergic is a new definition to treat the patients with moderate-to-severe asthma. The presence of negative prick test and presence or not of eosinophilia is an opportunity to use biologics to improve symptoms and quality of life [2–3]. The possible association of serum IgE levels with asthma, irrespective of specific allergic sensitization has long been investigated. Burrows et al. revealed that IgE-mediated mechanisms might play a role even in non-atopic asthmatics with no detectable allergen-specific IgE. Some studies have shown that up to 25% of adult asthmatics are non-allergic. We proposed to treat the patients according to different types [4–6] (Figure 1).

A minority of asthmatic individuals are not however demonstrably atopic by conventional criteria, which has led to the suggestion that asthma maybe divided clinically into atopic and non-atopic. Recently, there have been major advances in our understanding of the molecular mechanisms of non-atopic. Indeed, the mechanisms of this variant of asthma in which allergens have no obvious role in driving inflammatory process in the airways remain uncertain. This type of research will certainly point towards new types of mechanisms, which will allow a more personalized way to treat asthma [7].

3. Local and peripheral IgE synthesis in severe asthma

Non-atopic asthma patients are typically a late-onset condition, more common in females, and it tends to be more severe than atopic form, requiring higher doses of corticosteroids for

Cell types of epithelial components	Atopic asthma	Non-atopic asthma
Ciliated columnar	Damage ++	Damage +
Desmosomes	Breakdown ++	Breakdown +
Globlet cells	Hyperplasia (+)	Hyperplasia (-)
Basal cells	Damage +	Damage +
Basement membrane	Thickening ++	Thickening +
Eosinophils	Infiltration +++	Infiltration +++
Neutrophils	Infiltration +	Infiltration ++
Mast cells	Infiltration ++	Infiltration +
Lymphocytes	Infiltration +++	Infiltration ++
Macrophages	Infiltration +	Infiltration ++

**Table 1.** Comparison of bronchial epithelial components in atopic and non-atopic asthma.

adequate control. It often starts following a severe upper or lower respiratory tract infection or during pregnancy, but it also indicates that environmental factors may be more important in the causation of non-atopic asthma. The presence of increased local synthesis of IgE also in non-atopic asthmatics has been demonstrated in more recent studies. Ying et al. showed local expression of epsilon heavy chain of IgE in the bronchial mucosa in atopic and non-atopic asthmatics. Mouthuy et al. confirmed that local IgE production occurs in the bronchial mucosa in atopic asthma and showed for the first time, that this part of IgE is directed towards house dust mite allergens. [8–10].

We described in 2015, the presence of non-atopic phenotype in a population of 10 asthmatics in a cohort with omalizumab treatment in University Hospital of Puebla, Mexico. Since the identification of IgE as a major stimulus in the inflammation cascade, the development of agents to target IgE has thrived. [11] (**Table 1**).

#### 4. Anti-IgE drug omalizumab: mechanism of action

Omalizumab (OmAb) is a recombinant humanized monoclonal antibody that was designed to bind to IgE on the Fc (constant fragment) portion, C epsilon 3 locus, in the same domain where IgE is bound to FcRI. This drug was synthesized with the aim of sequestering free IgE and reducing allergic inflammation. This drug is administered subcutaneously and is absorbed slowly. The peak of serum concentration is reached after 7–8 days and it is eliminated via reticuloendothelial system having a half-life of around 26 days. It has been accepted for a long time that OmAb acts on the free IgE and abolish the binding of IgE to FcRI or FcRII, CD23 cells, B-cells, dendritic cells (DC), eosinophils (Eo), and monocytes. In several real-life studies, the use of OmAb has been associated with an absence of exacerbations and improvement in the quality of life, which is reflected in reduced hospital admissions and emergency visits but not in pulmonary function. The standard duration of treatment with OmAb has not been established to date. A follow-up study showed that after 6 years of OmAb treatment,

most patients have mild and stable asthma in the ensuing 3 years after treatment discontinuation, it has been suggested that the persistence of the effects of OmAb may be due to its ability to curtail airway remodeling in patients with asthma. In fact, it has been found that OmAb significantly decreased the airway wall area. After 1 year of omalizumab treatment, a significant mean reduction in eosinophilic infiltration was recorded as well as a reduction in the reticular base membrane in bronchial biopsies from patients with severe persistent allergic asthma was observed. These findings indicate that OmAb may modify the course of the disease due to their possible influence curtailing airway remodeling [12].

## 5. Anti-Immunoglobulin E in non-atopic asthma with omalizumab

In an attempt to elucidate the drug's mechanism of action, OmAb regulated FcRI expression negatively on basophils and plasmacytoid dendritic cells and increased forced expiratory volume in the first minute (FEV1) compared with baseline after 16 weeks in patients with severe non-atopic asthma demonstrated the possible role of IgE in non-atopic asthmatics [12–14]. The concept of Omalizumab treatment in non-atopic asthma is a new provocative idea and initially, some reports cases and data from severe asthma registries gave food for thought and discussion [15–16].

We concluded the functional role of local polyclonal IgE in airway mucosal tissue also in view of the finding of eosinophilic inflammation in nasal polyps with increased local tissue IgE levels independently of the allergic status of the patients. We presented the same case to Mexican female patient in University hospital of Puebla and showed the benefits of omalizumab in symptoms, QOL, and acute exacerbations, not in pulmonary function [13, 17].

## 6. Effects of omalizumab in non-atopic asthma patients

Eosinophilic asthma has been considered a phenotype of severe asthma. Allergic asthma can present with normal or increased numbers of eosinophils. The guidelines generally do not distinguish between the pathways responsible for the eosinophilia (atopic or non-atopic). Omalizumab can decrease the number of eosinophils in sputum on the bronchial mucosa and to a lesser extent in peripheral blood, in some cases, omalizumab fails to improve allergic asthma, this is probably due to the fact that the predominant physiopathological dysregulation comes initially from adaptive immunity, probably as a consequence of the highly intense activity of the allergic cascade. [18–19].

As a result of all these different modes of action, omalizumab has also been shown to interfere in certain stages of the remodeling process. [20–23]. Kutlu et al. described a case with 34 years old male patient the use of omalizumab with negative skin prick test and IgE in 203 U/L, they use omalizumab a dose of 225 mg every 2 weeks and after 6 months the patient was scored as 7 to 25 points at the asthma control test before the treatment of anti-IgE. We described and showed the improvement in non-atopic patients with omalizumab and started with 150 mg of omalizumab in our asthma Clinic in Puebla and increased the doses with excellent results [20–24].

7. Asthma-COPD overlap syndrome

Asthma and chronic obstructive pulmonary disease (COPD) are two common respiratory disorders which are associated with chronic inflammation or the airways. In text books, the two are described as distinct disorders, however, there is increasing awareness that in clinical practice many patients may have features of both. ACOS is a subset of patients with persistent airflow limitation who have clinical features of both asthma and COPD. (25).

Patients with ACOS have largely excluded from studies and hence information on their epidemiology, pathogenesis and treatment is sparse, we described in a COPD cohort from pneumology department in our asthma COPD clinic prevalence was 10 and 25% in asthma cohort. Another study described in COPD cohort has 15% of them fulfilling criteria for ACOS. Another study done in asthmatics who were smokers, found that 27% of them had ACOS. However, another study done showed that only 7% of asthma/COPD patients had ACOS. This wide variation can be partly attributed to the difference in the criteria used to diagnose ACOS in the above studies. The lack of consensus on a definition for ACOS has led to the wide range in prevalence varying between 11 and 56% among COPD, 13 and 61% among asthma, and 2% among the general population [25–30] (Tables 2 and 3).

Major criteria	Minor criteria
1. Persistent airflow limitation (post bronchodilator FEV1/FVC ratio < 0.70 of lower limit of normal) in individuals aged 40 years or older.	1. Documented history of atopy or allergic rhinitis.
2. At least 10 pack years of tobacco smoking or equivalent exposure to indoor or outdoor pollutants (biomass).	2. Bronchodilator response (BDR) using 400 mcg of albuterol/salbutamol >200 ml and 12% from baseline values on 2 or more visits.
3. Documented history of asthma before the age of 40 years or BDR >400 ml in forced expiratory volume in 1 s (FEV1).	3. Peripheral blood eosinophil count >300 cells/μL.
FVC = Forced vital capacity	
The criteria for diagnosis of ACOS consist of 3 major and 3 minor criteria. To diagnose ACOS, it is necessary to have 3 major criteria and at least 1 minor criteria.	

Table 2. Expert consensus major and minor criteria for ACOS.

Major criteria	Minor criteria
1. Very positive bronchodilator test (increase in FEV1 > 15% and >400 ml	1. High Level of total IgE
2. Sputum eosinophils	2. Personal history of atopy
3. History of asthma	3. Positive bronchodilator test on at least 2 occasions (increase of FEV1 > 12% and 200 ml).
For diagnosis at least 2 major criteria or 1 major criteria with 2 minor criteria.	

Table 3. SEPAR criteria for mixed COPD/asthma phenotype in COPD.



## 8. Recently use of biologicals for ACOS

In the past decade, interest in the clinical characteristics, importance and consequences for patients with overlapping features of asthma and COPD has been renewed. In their purest forms, asthma and COPD are distinct and readily recognizable clinical entities. Furthermore, guidelines for treatment of asthma and COPD are well established and evidence-based.

The unknowns continue to mount for patients in this overlap syndrome group who are unresponsive to existing treatments but continue to be symptomatic and at increased risk for exacerbations. The absence of treatment guidelines becomes particularly problematic when the use of biological is being considered. Experience with biological is most extensive with asthma, but studies of asthma treatments often exclude subjects with a history of smoking. Furthermore, in studies in COPD, a history of asthma is usually an exclusion criterion. Therefore, well recognized evidence-based guidance is largely absent as to what might be the best therapeutic approach, what patient characteristics are most predictive in selecting a specific next treatment or what outcomes are most likely to reflect treatment responsiveness. As many patients with asthma-COPD overlap syndrome might not achieve disease control with existing treatments, the consideration for and selection of a biological agent is an important unmet clinical need, both for the clinician and the affected patient [31].

Chest, Steven Maltby and colleagues at the University of Newcastle in Australia began to address this largely open question. What are the effects of omalizumab in this patient cohort? The Australian Xolair Registry was used to evaluate the real world use of omalizumab for severe uncontrolled allergic asthma. A total of 177 participants were evaluated and 17 of these had a doctor diagnosis of COPD. Omalizumab was found to be equivalently effective in patients with severe allergic asthma and a physician diagnosis of COPD, as well as severe asthma without COPD. In severe asthma and COPD, the asthma control questionnaire (ACQ) improved from 3.68 to 1.69 with the addition of omalizumab [31].

Initial studies have shown that omalizumab may be useful in patients with ACOS. It has been shown to improve symptoms, reduce exacerbations and hospitalization, and improve lung function parameters and reduced steroid requirement in these patients. However, larger randomized trial is required to further validate this observation. We presented the effects of omalizumab in ACOS patients with an excellent result in a group of 5 patients of the asthma COPD cohort clinic in University hospital of Puebla and showed improved lung function and symptoms [31–33].

Nayci et al. published the effectiveness of omalizumab treatment in asthma-COPD overlap syndrome in 2016 and described a clinical reduction in exacerbations and steroid requirement and improved symptoms and pulmonary function parameters in 6 patients. Dammert et al. published the use of Omalizumab in patients with COPD and atopic phenotypes in 7 cohort patients with positive allergy test and showed that omalizumab reduced the number of exacerbations, hospitalizations, and improved symptoms [34–35].

## 9. Conclusion

To conclude, there is now evidence suggesting that omalizumab improves patients with severe non-atopic asthma and ACOS. Therefore, it is important to review each patient meticulously and regularly and provide personalized and targeted treatment. In the case of using omalizumab to treat non atopic severe asthma, the evidence is conclusive in these phenotypes. In the era of personalized and targeted medicine, it is important to fully characterize our patients and prescribe treatment that aims at treating the particular patient to consider the cost-effectiveness. In this chapter, we described that omalizumab is efficient and safe to treat and improves and increases the quality of life.

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## Conflict of interest

None.

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