



# Omalizumab Therapy in Severe Allergic Asthma with Co-Morbidities during the COVID - 19 Pandemic - A Case Series

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**Abstract**

There is a dangerous liaison between severe asthma with co-morbidities and COVID-19 disease. There are several factors, which have been associated with increased risk for COVID-19 severity and mortality. Severe allergic asthma with co-morbidities such as poor lung function, adrenal suppression, recurrent nasal polyposis, food and drug hypersensitivity reaction in addition to older age, endocrine-metabolic and cardiovascular disease, have increased risk of hospitalization and mortality. We report three cases of severe asthma with co-morbidities: 1) Severe asthma with Chronic Rhinosinusitis with recurrent nasal polyposis and steroid dependency, 2) Asthma-COPD Overlap (ACO) and 3) Severe asthma with Lipid Transfer Protein Syndrome (LTPS) with NSAIDS hypersensitivity, infected by SARS-CoV-2, who were on concurrent Omalizumab therapy for more than a year had a favorable clinical course. They all could overcome COVID-19 disease without any significant consequences. We hypothesize, that treatment with Omalizumab for severe allergic asthma with co-morbidities is safe and might have potential anti-viral effect in COVID-19 disease.

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## Introduction

A COVID-19 pandemic has affected millions of people worldwide and has caused a substantial increase in hospitalizations for pneumonia with multiorgan disease, ARDS and death. Patients with severe Allergic Asthma disease with comorbidities carry an increased risk to common viral (human rhinovirus, influenza virus etc.) respiratory infections but not all these viruses affect patients equally. It has been a challenging task for the physicians due to increased risk of contracting SARS-CoV-2 infection and progression to severe COVID-19 disease. There is insufficient evidence to indicate which risk factors or comorbidities cause severe COVID-19 disease. During COVID-19 pandemic, not only older age, obesity, cardiovascular diseases, diabetes but also patients of severe allergic asthma co-morbid with poor lung function, recurrent nasal polyposis and steroid dependence with adrenal suppression and food & drug hypersensitivity reaction had increased risk of hospitalization and mortality [1].

Severe asthma phenotypes have differential impact on progression and severity of COVID-19 as in *Type 2- high* asthma endotype seems to have protective role in SARS-CoV-2 infection, while *Type 2 low asthma* endotype seems to confer an increased risk of infection and progression of COVID-19 diseases. Schlitz et al found that patients with severe asthma taking high dose Inhaled Corticosteroids (ICS) had 55% increased risk of death from COVID-19 [2,3].

Whether biologicals are detrimental, neutral or beneficial during COVID-19 pandemic in severe asthma infected with SARS-CoV-2, the decision should be a case-by case discussion supported by a multi-disciplinary team. There is no evidence that biological therapy suppresses immunity in severe allergic asthma with co-morbidities. The guidelines (WAO/GINA/EAAACI/ERS/BTS etc.,) recommend the continuing of biologicals as usual in patients with proven SARS-CoV-2 infection by weighing the benefits and risk individually [4,5]. It not only decreases the risk of SARS-CoV-2 infection but also decreases progression of COVID-19 disease. Omalizumab is the only biological with proven antiviral action against viruses responsible for upper respiratory tract infections and asthma exacerbations [1]. In PROSE study (preventive Omalizumab or step-up therapy) for severe fall exacerbation, Omalizumab therapy was able to decline rhinovirus infection duration, viral clearance and illness frequency [6].

We report three cases of severe asthma with co-morbidities, *case 1*-Severe asthma with Chronic Rhinosinusitis with recurrent nasal polyposis and steroid dependency, *case 2*- Asthma-COPD Overlap (ACO) and *case 3*- Severe asthma with Lipid Transfer Protein Syndrome (LTPS) with NSAIDS hypersensitivity. All three cases had SARS-CoV-2 infection and were on concurrent use of Omalizumab for more than a year. They all could overcome COVID-19 disease without any significance consequences.

We did not hesitate to continue Omalizumab therapy in our patients because they did not have a severe and/or complicated SARS-CoV-2 infection and recovered rapidly with concurrent Omalizumab therapy. We hypothesize, that in severe asthma associated with co-morbidities, Omalizumab should be seen as more of an immune modulator and organizer of our immune system & has potential effect as an anti-viral in SARS-CoV-2 infection.

## Case presentation

### Case I

18 years old male patient was diagnosed with *severe asthma* with Chronic Rhinosinusitis with recurrent *nasal polyposis and steroid dependency* 5 years ago. He had frequent symptoms despite high dose Oral Corticosteroids (OCS) [Budesonide/Formoterol (320/9ug) X twice a day] requiring short courses of OCS. He underwent multiple surgical interventions for recurrent nasal polyps. Allergy evaluation revealed immunologically significant positivity to *Alternaria alternata* [Skin Prick Test (SPT)-10mm/ Specific IgE- 93Kua/l] and *Aspergillus fumigatus* (SPT-6mm, Specific IgE- 27.7Kua/L). Total IgE-3422 IU/mL, Absolute Eosinophil Count (AEC) was 710 cells/ul (Table 1). Pulmonary Function Test (PFT) confirmed significant reversibility with bronchodilator (>20% increase in FEV1). PNS and Endoscopy revealed opacification of maxillary sinus and polyps. Asthma Control Test (ACT) score was 15. We additionally started combined allergen immunotherapy with omlizumab-150mg which resulted in prompt clinical benefit and resolution of asthma symptoms, ACT improved to 23. A week after he received the 17<sup>th</sup> dose of his monthly omalizumab, he came with suspected case of COVID-19 after one of the family members tested positive. He had excessive fatigue as the sole symptom. His diagnosis was confirmed by RT-PCR test for SARS-CoV-2 despite his clear chest X-ray. In accordance with national protocols, he was informed about the progression and treatment of the disease and was sent home for self-quarantine. We suggested pausing Omalizumab treatment but educated the patient about continuing his inhaled regimens [Budesonide/Formoterol (320/9ug) for asthma control. During this period, he suffered muscle pain, mild coughing. He had no asthma exacerbation and did not need frequent relievers or OCS (Oral Corticosteroids). His COVID-19 treatment included symptomatic treatment, Ivermectin and Azithromycin for 5 days. After his symptoms receded, we confirmed his recovery by a negative RT-PCR after the 10th day of COVID-19 symptoms. He was then permitted to work and his Omalizumab treatment was reinitialized for the next month 20 days after a negative RTPCR test.

### Case II

70 years old woman was diagnosed with Asthma-COPD Overlap (ACO) with clinical features of severe allergic asthma with irreversible airflow obstruction, (FEV1/FVC- 65%), Poor Peak Flow Variability (PEFR) (150-200L/min). Asthma onset was reported by the age of 30 years. Allergy evaluation revealed immunologically significant positivity to *Dermatophagoides pteronyssinus* (DP) (SPT- 8mm/specific IgE- 0.54kUA/l) and *Dermatophagoides farinae* (DF) (SPT- 8mm, specific IgE- 0.65Kua/L) and Total IgE was 264 IU/mL (Table 1). She had frequent symptoms despite high dose of LABA (Long Acting Beta Agonist), LAMA (Long Acting Muscarinic Antagonist), ICS (Inhaled Corticosteroids), deriphylline 300 mg and 10 mg of maintenance dose of Methylprednisolone (MP) per day. Weaning of MP was unsuccessful because of asthma relapse. She suffered from prolonged exhalation, wheezing and shortness of breath despite her medications. We decided to administer monthly injections of Omalizumab. Omalizumab was well tolerated and asthma control symptoms were evaluated by his morning PEFR values (increased from 150L/min to 350L/min) and ACT score increased from 12 to 19. We were able to stop OCS after 12 months. After her 43<sup>rd</sup> Omalizumab injection, she came with complaints of dry cough and tightness of chest. Her diagnosis was confirmed by RT-PCR test for COVID-19 after 15<sup>th</sup> day of last

Omalizumab dose, although her chest X-ray did not show any sign of infection. On physical examination wheeze was detected bilaterally. Her Omalizumab treatment was suspended. The progress of the disease was explained to her and she was sent home for self-quarantine. During this time, no other symptom was detected and her asthma stayed under-control. Her COVID-19 medications included azithromycin, doxycycline and OCS for 5 days along with supportive therapy of ACO. We confirmed her recovery by a negative RT-PCR after the 10<sup>th</sup> day of COVID-19 symptoms. Her routine treatment with monthly Omalizumab was continued after her symptoms were well controlled. She could overcome COVID-19 disease without any significant consequences.

### Case III

32 years old woman was diagnosed with Severe asthma with Lipid Transfer Protein Syndrome (LTPS) with NSAIDs hypersensitivity with signs and symptoms of urticaria, angioedema and anaphylaxis after intake of diclofenac (NSAIDs). She had been on high dose ICS, LABA, LAMA, anti-histamines and on & off OCS with no relief. Allergy evaluation revealed immunologically significant positivity to *Prosopis juliflora* (SPT-6mm,

*specific IgE-3.65Kua/l*), *Haloptelea intergrifolia* (SPT-6mm, *specific IgE-3.39Kua/l*), DP (SPT-8mm, *specific IgE- 32.20Kua/l*), DF (SPT- 8mm, *specific IgE-3.71Kua/l*) and Prick-Prick Test (PPT) was positive for peach pulp-3mm, peach peel-4mm, Total IgE was 249IU/mL and AEC was 500cells/uL (Table 1). OCS provided temporary relief. We decided to administer monthly injections of Omalizumab. Omalizumab was well tolerated and asthma control symptoms were evaluated by her morning PEFr values (increased from 300L/min to 500L/min) and ACT score increased from 18 to 24. After her 12<sup>th</sup> injection of Omalizumab, she presented to our clinic with complaints of dry cough and fatigue. Her diagnosis was confirmed by RT-PCR test for COVID-19, although her chest X-ray did not show any sign of infection. Her Omalizumab treatment was suspended. The progress of the disease was explained to her and she was sent home for self-quarantine. During this time, no other symptom was detected and her respiratory and skin symptoms were under-control. Her COVID-19 medications included Ivermectin and Azithromycin and there was no need for additional regimens. We confirmed her recovery by a negative RT-PCR after the 10th day of COVID-19 symptoms. Her routine treatment with monthly Omalizumab was continued after her symptoms resolved.

**Table 1:** Clinical characteristics.

	CASE I		CASE II		CASE III	
	BEFORE COVID 19	AFTER COVID19	BEFORE COVID 19	AFTER COVID19	BEFORE COVID 19	AFTER COVID19
ACT	23	24	19	19	24	24
Total IgE	3422 IU/mL	ND	264 IU/ml	ND	249 IU/mL	ND
FEV1	95%	95%	14%	35%	86%	106%
FEV1/FVC	86.5%	88%	70%	70%	70.4%	81.5%
PEFR	550 L/min	550 L/min	350 L/min	370 L/min	500 L/min	550 L/min
AEC	363 cells/uL	80cells/uL	0 cells/uL	0 cells/uL	120cells/uL	120 cells/uL
SPT/ specific IgE	Alternaria alternata- 10mm/ 93 Kua/l Aspergillus fumigatus-6mm/27.7 Kua/L		DP-8mm/ 0.54 Kua/l DF-8mm/ 0.65 Kua/L		Prosopis-6mm/ 3.65 kua/L H. intergrifolia-6mm/ 3.39 Kua/L DP-8mm/ 32.2 Kua/l DF-8mm/ 3.71 Kua/L	
Regular Treatment	ICS+LABA+LTRA+AIT +OMZ		ICS+LABA+LAMA+LTRI +Anhydrous deriphylline +OMZ		ICS+LABA+LAMA+LTRI+OMZ	

AEC: Absolute Eosinophil Count; SPT: Skin Prick Test; DP: D. pteronnyssinus; DF: D. farinae, ICS: Inhaled Corticosteroids; LABA: Long-Acting Beta Agonist; LTRA: Leukotriene Receptor Antagonist; AIT: Allergen Immunotherapy; LAMA: Long Acting Muscarinic Antagonist; OMZ: Omalizumab.

### Discussion

Common viruses responsible for acute asthma are human rhinovirus (76% in children and 83% in adults), influenza virus, while coronavirus, adenovirus, parainfluenza virus, metapneumovirus, bocaviruses are responsible to a lesser extent. Asthmatics are at a greater risk of Community Acquired Pneumonia (CAP, bacterial and viral), almost 2-folds in asthmatics compared with healthy control subject [2]. The novel coronavirus, SARS-CoV-2 is currently spreading around the world. It is major public health problem in patients of chronic diseases with co-morbidities. According to recent guidelines, there is no supplementary risk of SARS-CoV-2 viral infection or severe clinical forms of COVID-19 disease in asthmatic patients as long as their asthma is well controlled with optimal therapy [7,8]. There is a dangerous

liaison between uncontrolled severe asthma with co-morbidities and COVID-19. There is insufficient evidence to indicate which co-morbidity causes severe and progressive course of COVID 19 disease. As of now, no studies have been published on patients with severe asthma, specially treated with monoclonal antibodies (biologicals) which could impair the immune response or increase susceptibility to viral infection, except a few case studies. On the other hand, if we discontinue biologicals, in patients with severe asthma, there is increased risk of asthma exacerbation resulting in greater need of OCS and hospitalization, which may further increase the risk of exposure or infection to SARS-CoV-2. That is why; all international guidelines have agreed not to discontinue ongoing biological treatment for the control of asthma during COVID-19 pandemic [9].

Bronchial asthma is the most important allergic indication for biological targeting IgE and Type II-high inflammation. The author has published the benefits of Omalizumab therapy as a Steroid Sparing Effect in Stage IV (Corticosteroid Dependent) Allergic Bronchopulmonary Aspergillosis [10]. Allergic asthma is mostly characterized by type 2-high inflammation and allergic sensitization is inversely related to Angiotensin Converting Enzyme II (ACE-II) expression. As a result, allergic patients under-express ACE-II on airways and could be less prone to suffer from COVID-19. Moreover, high eosinophil count could also reduce the susceptibility to COVID-19. Allergic asthmatics produce lower level of Type I Interferon (INF) or other cytokines to protect from viral infection by plasmacytoid dendritic cells and epithelial cells. Now described as cross-regulation mechanism of FcεRI, and TLRs as cross-linking of IgE bound to FcεRI, by allergens, results in reduced TLR expression. Ultimately, there is decrease capacity to secrete type I interferons for viral defense. Omalizumab has shown to downregulate the high affinity IgE receptor on Plasmacytoid Dendritic Cells (pDC), essential for anti-viral immune exposure. It blocks pro-inflammatory cytokines such as IL-1, IL-6 and IL-33 etc., and indirectly reduces the release of inflammatory agents such as histamine and leukotrienes etc., in addition to anti-viral effect. The clinical efficacy and safety of Omalizumab allows great improvement in the management of asthma and leads to a great increase in the quality of life and productivity of patients [11,12].

We had seventeen severe asthma patients on Omalizumab therapy. Only eight of them had COVID-19 disease during the pandemic. None of these COVID-positive patients reported any asthma exacerbation during their quarantine period. These cases had mild symptoms with no fever or breathlessness, no X-ray findings diagnostic of COVID-19 and no additional need of OCS for COVID-19 except one patient who was given low dose of OCS for 5 days. In our three cases, currently being treated with Omalizumab for more than 12 months having Th2-high inflammation (immunologically significantly positive to perennial allergens by SPT and specific IgE) and one of them had high eosinophil count. They were well controlled with additional therapy with Omalizumab and case 1 was given combined allergen immunotherapy and Omalizumab. None of them suffered from progressive or severe COVID-19 disease and recovered rapidly.

### Conclusion

Our three cases of 1) Severe asthma with Chronic Rhinosinusitis and recurrent nasal polyposis and steroid dependency, 2) Asthma-COPD overlap (ACO) and 3) Severe asthma with Lipid Transfer Protein Syndrome (LTPS) with NSAIDS hypersensitivity suggest that continuing treatment with Omalizumab is safe during COVID-19 pandemic. This is in line with global guidelines and positioning papers that have recommended not stopping treatment with biologicals in mild to moderate COVID-19 course. We need further studies that biologicals like Omalizumab for severe asthma with co-morbidities not only decrease the risk of SARS-CoV-2 infection but also decrease the progression of COVID-19 disease and might even be protective.

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