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Omalizumab: what do we learn from patients in treatment for more than ten years?

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TO THE EDITOR:

In recent years, several studies have examined the use of biologic agents in the treatment of asthma. Omalizumab is a humanized anti-IgE monoclonal antibody and the first biologic agent to be approved for use in the treatment of asthma. It is currently licensed for use in adults and children ≥ 6 years of age with severe uncontrolled allergic asthma.[1] By binding to circulating free IgE, omalizumab prevents it from interacting with its high- and low-affinity receptors on mast cells, basophils, and circulating dendritic cells, thus interrupting the inflammatory cascade and the release of proinflammatory mediators.[1] Several studies have confirmed the efficacy and safety of omalizumab in patients with severe allergic asthma, even after long-term use.[2-4]

The present report describes the clinical and functional efficacy of omalizumab, as well as its safety, in two nonsmoking women with severe asthma receiving treatment with the drug for more than 10 years. The diagnosis of asthma was based on clinical criteria (asthma symptoms appearing in childhood and triggered/worsened by aeroallergens and environmental irritants), as well as on positive aeroallergen-specific IgE and expiratory flow limitation, as assessed by an FEV_1/FVC ratio of < 75% of the predicted value. One of the patients (patient 1) showed bronchodilator reversibility during follow-up, albeit only once. Despite receiving regular treatment with high-dose inhaled corticosteroids and a long-acting β_2 agonist, neither patient achieved disease control as defined by Global Initiative for Asthma criteria.[5] Both had at least 5 exacerbations per year and used daily short-acting β_2-agonist medications and long-term systemic corticosteroids. Over the course of 1 year, both patients used systemic corticosteroids on more than 50% of the days, patient 1 using prednisone at a dose of 10 mg/day and patient 2 using betamethasone at least six times a year. All comorbidities potentially contributing to poor asthma control were treated, the exception being obesity. Treatment adherence and inhaler technique were evaluated at each visit. The patients were followed for more than 1 year but failed to achieve disease control with conventional therapy, omalizumab therefore being added to the treatment regimen. The addition of omalizumab reduced exacerbations and eliminated the need for emergency room visits and hospitalizations, systemic corticosteroid therapy therefore being discontinued. Patient clinical and laboratory data, as well as lung function parameters, are shown in Table 1.

Response to omalizumab occurs within the first few months of treatment, and the benefits of omalizumab in reducing exacerbations, emergency room visits, and hospitalizations are well established.[2] Recent studies have shown the safety and efficacy of long-term treatment with omalizumab.[3,4] There is controversy regarding the benefits of omalizumab in reducing the use of inhaled corticosteroids over the course of treatment; there have been reports of small to moderate reductions in use,[2,3,6] as was the case here. In addition, there have been reports of reductions in the use of long-acting β_2 agonists and montelukast after treatment for more than 60 months.[7] The fact that omalizumab results in a more significant reduction in or discontinuation of systemic corticosteroids reinforces the benefits of the drug in controlling inflammation, reducing the risks and adverse effects associated with frequent or prolonged use of systemic corticosteroids.[6] In the two cases reported here, the addition of omalizumab to the treatment regimen allowed the patients to discontinue systemic corticosteroid therapy. With regard to lung function, changes in spirometric parameters are variable. Although some studies have shown an increase of 6.7-11.4% in FEV_1 after 4-6 months of treatment,[2] others have shown a time-dependent response, with increases of 15% and 24% after 36 months and 48 months, respectively.[3,8] However, most studies have shown that FEV_1 increases after approximately 12 months of treatment, at which time omalizumab reaches its peak efficacy, drug efficacy remaining constant or slightly decreasing thereafter. In a study involving 24 severe asthma patients using omalizumab, there was a significant increase in mean FEV_1 (in % of the predicted value), from 37.6% at the beginning of treatment to 44.0% at treatment week 16.[9] In the two cases reported here, FEV_1 and FVC varied over the years, having improved in patient 1. In patient 2, there was an increase in FVC; however, FEV_1 remained unchanged. Nevertheless, despite treatment, severe obstructive lung disease persisted in both patients. Airway remodeling and irreversible airway changes are likely responsible for the lack of functional improvement in some patients. The patients in the present study had been living with asthma and frequent exacerbations for more than 40 years, the latter being a risk factor for airway remodeling.[10] It has been suggested that, by effectively reducing exacerbations, omalizumab can indirectly reverse the structural changes induced by periods of worsening airway inflammation, thus slowing lung function decline.[7]

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Table 1. Demographic, clinical, laboratory, and spirometric data for two severe asthma patients receiving treatment with omalizumab for more than 10 years.

Variable	Patient 1	Patient 2
Age, years	65	56
Sex	Female	Female
BMI, kg/m^2	37.1	34.6
Duration of asthma, years	61	41
Duration of treatment with omalizumab, years	11	11
Family history of asthma	No	Yes
Emergency room visits and hospitalizations for asthma in the year preceding treatment	Yes	Yes
ICU admission prior to treatment initiation	Yes (EI)	No
Emergency room visits and hospitalizations for asthma after treatment initiation	No	No
Mean inhaled corticosteroid dose prior to treatment initiation (budesonide, µg/day)	1,200	1,200
Mean inhaled corticosteroid dose after treatment initiation (budesonide, µg/day)	800	800
Continuous systemic corticosteroid use prior to treatment initiation	Yes	Yes
Adverse events during treatment with omalizumab	No	No
Comorbidities	Obesity, rhinitis, GERD, SAH	Obesity, rhinitis, GERD, DM
Peripheral eosinophil count, cells/mm^3	113	248
Total IgE, IU/mL	313	192
Aeroallergen-specific IgE, skin prick test for aeroallergens, or both[a]	Positive for *D. pteronyssinus*, *D. farinae*, *B. tropicalis*	Positive for *D. pteronyssinus*, *D. farinae*, *B. tropicalis*
Pre-BD FVC, L (%P)[b]		
At the initiation of treatment with omalizumab	1.00 (42)	1.79 (58)
After 5 years of treatment	1.19 (51)	2.36 (75)
After 10 years of treatment	1.29 (60)	2.07 (70)
Pre-BD FEV_1, L (%P)[b]		
At the initiation of treatment with omalizumab	0.44 (23)	0.90 (36)
After 5 years of treatment	0.62 (32)	1.38 (54)
After 10 years of treatment	0.62 (37)	0.85 (38)
FEV_1/FVC, n (%P)[b]		
At the initiation of treatment with omalizumab	0.44 (55)	0.50 (62)
After 5 years of treatment	0.52 (64)	0.58 (72)
After 10 years of treatment	0.48 (61)	0.41 (51)
HRCT of the chest	Bronchial wall thickening	Bronchial wall thickening

BMI: body mass index; EI: endotracheal intubation; GERD: gastroesophageal reflux disease; SAH: systemic arterial hypertension; DM: diabetes mellitus; *D.*: *Dermatophagoides*; *B.*: *Blomia*; BD: bronchodilator; and %P: in percentage of the predicted value. [a]Aeroallergens tested: *D. pteronyssinus*, *D. farinae*, *B. tropicalis*, *Aspergillus fumigatus*, dog dander, and cat dander. [b]Long-acting β_2 agonist use was temporarily discontinued at least 12 h before spirometry.

In the present study, neither patient experienced adverse local or systemic effects during treatment with omalizumab, which was shown to be safe. There are conflicting data regarding the adverse effects of omalizumab, most of the data being from earlier studies.[2]

One of the limitations of the present study is that neither clinical disease control nor quality of life was objectively assessed with the use of standardized questionnaires, such as the Asthma Control Test and the Asthma Quality of Life Questionnaire. Observational studies using such instruments have shown a significant improvement in asthma control and quality of life after 1 year of treatment with omalizumab, with a slight but continuous improvement during 4-5 years of follow-up.[2]

In conclusion, long-term treatment with omalizumab appears to be safe and effective. Even after 10 years of treatment, omalizumab produces sustained benefits, including a slowing of the rate of decline in lung function.

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