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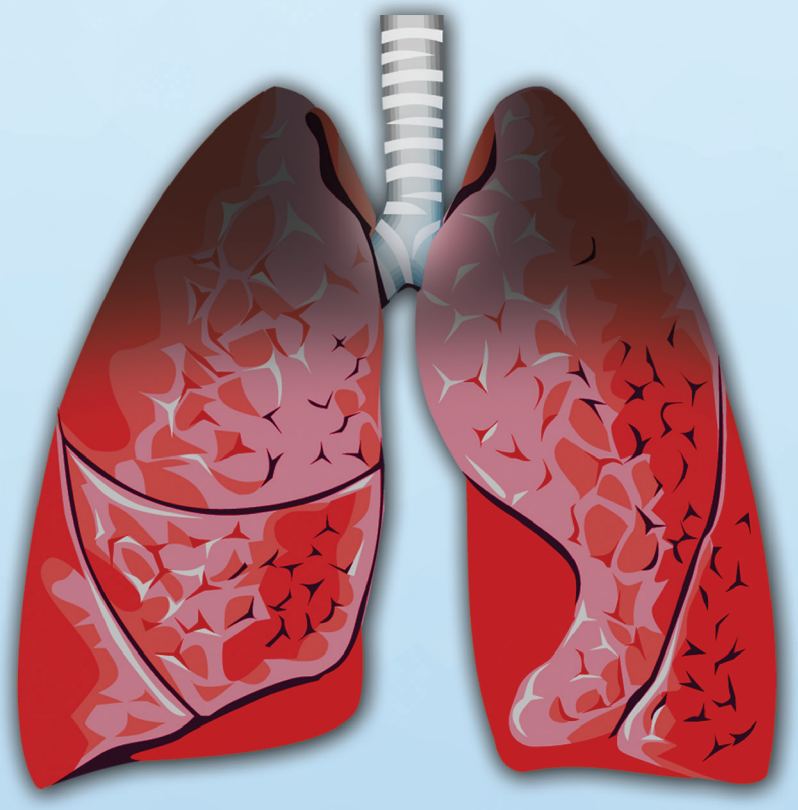

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# Omalizumab as a long-term treatment for patients with severe asthma. Is it safe?: a ten-year study

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**Background**
anti-IgE (Omalizumab) is one of the targeted therapies for severe bronchial asthma. Its real-life safety is still under scrutiny.
The aim of the study was to evaluate the persistent efficacy and safety of Omalizumab as a long-term treatment of severe bronchial asthma.
**Patients and methods**
A prospective cohort study was conducted on 74 patients who had severe bronchial asthma eligible for Omalizumab subcutaneous treatment with a long-term regular follow-up to evaluate the long-term safety and efficacy of Omalizumab.
**Results**
This study was conducted on 74 patients who had severe bronchial asthma: 33 patients (44.6%) were males with a mean±SD (37.2±4), and 41 females (55.4%) with a mean±SD (35.9±6). Those patients were eligible for Omalizumab treatment with a long-term regular follow-up (from 7 to 10 years) to assess the long-term safety of Omalizumab. Omalizumab treatment has a significant improvement in the clinical condition of severe bronchial asthma as it decreased the number of patients who used oral steroids from 63 patients (before starting treatment) to 6 patients after 6 months of treatment, and 2 patients after 12 months of the dose. The use of tiotropium bromide had a significant decrease because the number of patients fell from 61 patients (before the start of treatment) to 13 patients after 6 months. It also reduced the number of acute exacerbations of bronchial asthma from 7 times per year (before the start of treatment) to 3 times after 6 months, and 2 times after 12 months of treatment. Patients' pulmonary functions (FEV1, FEV1/ FVC, PEFR) improved significantly from (43.7±9, 52.3±11, 51.1±4) before starting Omalizumab treatment to (64.1±11,71.3±13, 68.2±7) after 6 months of usage; and to (69.4±12, 73.3±14, 72.1±6) after 12 months of treatment. Long-term use of Omalizumab has less severe side effects as 70% of patients had injection site reactions in the form of local tenderness and swelling, 24.3% had a headache, 12% had nausea, 9.4% had myalgia, and 17.5% had a fever while the serious side effects as cancer, anaphylaxis or myocardial infarction has not recorded. All the side effects occurred in the first year of treatment.
**Conclusion**
Long term use of Omalizumab in severe bronchial asthma management has persistent efficacy and no serious side effects such as cancer, myocardial infarction or anaphylaxis and has only minimal side effects that occurred mostly in the first year of Omalizumab treatment, meaning that the physician cannot stop giving patients the medication.

**Keywords:**
anti-IgE, long-term treatment and side effects, Omalizumab, safety, severe asthma

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## Introduction

Severe bronchial asthma treatment has made very rapid steps of development due to deep inside works for understanding the complex interactions between immunological, genetic and environmental factors, with different endotypes and phenotypes. For more than fifteen years ago, the first biological treatment for severe bronchial asthma was Omalizumab [1]. Since then, many of results has reported both on its long-life safety and efficacy. Over time; An excellent safety and efficacy results has been established, even in complicated patients and under special situation as the use of Omalizumab in pregnant women with severe asthma. Inspite of the long-life safety and efficacy of Omalizumab have been established, increasingly

longer follow-up studies can further reestablish these results and may be new results appear, for example, on any decrease of efficacy or develop of any unexpected adverse effects. This study aimed to assess the persistence of the efficacy and safety of Omalizumab as a long-term treatment of severe bronchial asthma after 10 years of treatment.

## Patients and methods

A prospective study was conducted on 74 patients (33 males (44.6%) with a mean score of ±SD (37.2 ± 4); and 41 females (55.4%) with a mean of ±SD (35.9 ± 6) who had severe bronchial asthma, and they were eligible for Omalizumab subcutaneous treatment. The first patient was enrolled in June 2012 while the last one was enrolled in August 2015.

## Severe asthma diagnosis and treatment were conducted in line with the GINA guidelines.

**Patients who had severe bronchial asthma or other chronic allergic conditions are divided as follows:**

(1) 33 patients (44.6%) had severe asthma only;
(2) 41 patients (55.4%) had severe asthma and allergic rhinitis;
(3) 13 patients (17.5%) had severe asthma, allergic rhinitis and chronic atopic dermatitis; and
(4) 7 patients (9.4%) had severe asthma, allergic rhinitis, chronic atopic dermatitis and chronic allergic conjunctivitis.

## All patients went through:

(1) a medical history check: especially respiratory symptoms as cough, dyspnea, chest wheeze and tightness that has variability over time and in intensity.
(2) body weight, height and body mass index measurements;
(3) complete blood picture to measure eosinophil count;
(4) total immunoglobin E (IgE);
(5) lung function testing by computerized spirometry with a Sensor medics Vmax 229 (Sensor medics, Yonda Linda, CA, USA) done for all patients for measuring FEV1, FVCFEV1/FVC%, PEF, and MVV with reversibility test to confirm variable expiratory airflow limitation.
(6) the asthma control test ACT has 5 items (respiratory symptoms, daily activities, use of rescue medications, and overall self-assessment of asthma impact) which is a self-administered tool that identifies patients' asthma control level; the ACT scores range from 5 (the asthma is poor controlled) to 25 (the asthma is well-controlled). A score of >19 indicates the control of asthma is optimal [2,3].

Inclusion criteria: any patient (over 18 years of age) with severe bronchial asthma and was eligible for Omalizumab treatment according to GINA guidelines [4] patients were excluded due to they refused their medical data to be disclosed for research purposes.

### Omalizumab

The dose of Omalizumab was calculated through Omalizumab drug chart in severe bronchial asthma above 18 years according to IgE level and body weight of the patient. (EMA/Xolair2009) [4].

## The dose of Omalizumab ranged from (300 mg to 1200 mg) as follows:

(1) patients took 300 mg per month;
(2) (4) patients took 300 mg every other week;
(3) (11) patients took 450 mg per month;
(4) (28) patients took 450 mg every other week;
(5) (21) patients took 600 mg monthly; and
(6) patients took 600 mg every other week.

The dose was given to patients subcutaneously in one-day care by trained nurses under the supervision of a doctor.

The total number of dosages of Omalizumab taken was 10752. Patients were observed by the nurse and the doctor for 2 h after taking Omalizumab in case there were any immediate side effects.

### Follow up

Patients paid regular visits to the outpatient chest clinic every other month. Patients were also asked to contact us in case of an emergency so that we could record any side effects related to Omalizumab medication.

Reassessing the patients' conditions After (6,12, 48, 120) months especially the use of oral corticosteroid, the dose of inhaled steroids, use of anticholinergic (tiotropium bromide hand haler), level of asthma control by ACT, number of acute exacerbations of bronchial asthma, number of hospital admissions, level of IgE, any side effect related to Omalizumab medication, and pulmonary function tests: (FEV1, FEV1/FVC, PEFR, FVC).

### Ethical consideration

The privacy, rights, well-being, and health of the participants were protected through informed consent, which they were asked to read and sign in case they agreed to participate in the study.

### Data analysis

Analysis of the data was performed using SPSS version 25 for Win-downs. Results are expressed as mean and standard deviation. Descriptive data were tabulated. Quantitative variables are presented as normally distributed variables or as medians and interquartile range (IQR). The 95% confidence intervals are indicated for each of the three-outcome end-points. The *P* value has statistically significant if the value is less than 0.05.

**Table 1 Demography and some parameters of the patients**

| no | Parameter | No and % |
|---|---|---|
| 1 | Age | |
| 2 | Sex: | |
| | Male: | 33 (44.5%) |
| | Female: | 41 (55.5%) |
| 3 | Body weight | 66.8±5 |
| 4 | Hight | 159.9±7 |
| 5 | Body mass index (BMI) | 25.4±10 |
| | Smoking H: | |
| | Nonsmoker: | 22 (29.7%) |
| | Ex-smoker: | 9 (12.1%) |
| | Heavy smoker: | 14 (18.9%) |
| | Moderate smoker: | 16 (21.7%) |
| | Mild smoker: | 13 (17.6%) |
| 6 | Comorbid: | |
| | Allergic rhinitis: | 41 (55.4%) |
| | Sinusitis | 23 (31%) |
| | Chronic Atopic dermatitis | 13 (17.5%) |
| | Chronic allergic Conjunctivitis | 7 (9.4%) |
| | Obesity | 22 (29.7%) |
| | Hypertension | 37 (50%) |
| | Diabetes mellitus | 12 (16.2%) |
| | Gastro esophageal reflux disease. (GERD) | 5 (6.7%) |

There was 33 male patients while 41 were female. The mean and SD of the body weight of the patients were (66.8±5). Regarding smoking habits: 29.7% were nonsmokers, 12.1% were ex-smokers and 8.9%, 21.7%, and 17.6% were heavy, moderate and mild smokers respectively. Most common comorbidity was allergic rhinitis and hypertension (from 55% to 50%), while GERD and allergic Chronic allergic Conjunctivitis were about 10.5%.

## Results

The study was conducted on 74 patients who had severe bronchial asthma and they were eligible for Omalizumab subcutaneous treatment from (1-6-2012 to 30-8-2022).

There were 33 male patients while 41 were female. The mean and SD of the body weight of the patients were (66.8±5). Regarding smoking habits: 29.7% were nonsmokers, 12.1% were ex-smokers and 8.9%, 21.7%, and 17.6% were heavy, moderate and mild smokers respectively. Most common comorbidity was allergic rhinitis and hypertension (from 55% to 50%), while GERD and allergic Chronic allergic Conjunctivitis were about (10.5%) (Table 1).

There was a significant improvement of some clinical parameters after (6, 12, 48 and 120) months of Omalizumab treatment such as the use of (OCS, ICS, tiotropium bromide), the number of (acute exacerbations and hospital admissions for the last year), and pulmonary functions. IgE increased in the first year of Omalizumab treatment, but there was a significant decrease in its level after that (Table 2).

The most common side effect was injection site reaction as tenderness and local swelling was about 70%, while headache, Nausea, myalgia and fever were less common, about 10.8%, 5.4%, 4%, and 8.1%, respectively. The complications were common in the first year. The serious side effects as cancer, anaphylaxis and myocardial infarction were not reported (Table 3).

**Table 2 Some clinical parameters and pulmonary function tests before and (6, 12, 48 and 120) months after Omalizumab treatment**

| Parameters | Before omalizumab treatment | After 6 months from treatment | After 12 months from treatment | After 48 months from treatment | After 120 months from treatment | *P* value |
|---|---|---|---|---|---|---|
| Use of oral steroid (OCS) | 63(85%) | 6(8%) | 2(2.7%) | - | - | <0.0001 |
| Use of tiotropium bromide | 61(82.4%) | 13(17.5%) | 3(4%) | - | - | >0.0001 |
| ACT test | 11.2±5 | 22.1±7 | 23.4±5 | 23±2 | 24±1 | <0.0001 |
| No of acute exacerbation/last year | 9.4±5 | 17.5±3 | 1.7±2 | 1.1±3 | 0.3±1 | 0.001 |
| No of hospital admission/ last year | 7.8±5 | 3.1±4 | 1.5±3 | 1.2±2 | 1.1±1 | <0.001 |
| Use of high dose of (ICS) inhaled steroid | 74(100%) | 41(55.4%) | 14(18.9%) | 11(14.8%) | 7(9.4%) | <0.000 |
| Serum total IgE | 473.5±23 | 598.7±11 | 688.7±13 | 301.7±12 | 212±11 | <0.001 |
| Pulmonary function test: | | | | | | |
| FEV1 | 43.7±9 | 61.4±7 | 71.4±8 | 72.1±4 | 76.2±5 | <0.001 |
| FEV1/ FVC | 52.4±11 | 74.8±7 | 78.4±4 | 79.1±8 | 80.3±9 | >0.001 |
| PEFR | 56.7±9 | 68.7±8 | 73.4±7 | 74.1±7 | 78.6±8 | >0.00 |
| FVC | 85.1±7 | 86.1±4 | 84.1±7 | 86.11±7 | 89.1±5 | >0.001 |

There was a significant improvement of some clinical parameters after (6,12,48) months from omalizumab treatment as use of (OCS, ICS, tiotropium bromide), no of (acute exacerbation and hospital admission/ last year) and pulmonary functions. While IgE was increasing in the first year of omalizumab treatment and after that was significant decrease of the IgE level.

**Table 3 Long term Side effects of Omalizumab treatment**

| Side effect | During 6month | Between 6-12 months | Between 1-4 years | After 4 years |
|---|---|---|---|---|
| Injection site reaction | | | | |
| Tenderness | 28 (37.8%) | 19 (25.7%) | 8 (10.8%) | 9 (12%) |
| Swelling | 24 (32.4%) | 20 (27%) | 14 (18.9%) | 12 (12.2%) |
| Headache | 8 (10.8%) | 5 (6.7%) | 3 (4%) | 2 (2.7%) |
| Nausea | 4 (5.4%) | 2 (2.7%) | 3 (4%) | ------ |
| Myalgia | 3 (4%) | 1 (1.3%) | 2 (2.7%) | 1 (1.3%) |
| Fever | 6 (8.1%) | 3 (4%) | 3 (4%) | 1 (1.3%) |

Showed some side effects of Omalizumab treatment; the most common side effect was injection site reaction as tenderness and local swelling about 70% while headache. Nausea. myalgia and fever were less common about (10.8%5.4%4%, 8.1%) respectively. The complications were common in the first year.

**Table 4 Coefficient of contingency for side effects with some parameters**

| Parameters | *R* | *P* |
|---|---|---|
| Dose of the Omalizumab. | 0.26 | 0.12 |
| Frequency of the Omalizumab. | 0.19 | 0.21 |
| Smoking history: | | |
| Non smoke | 0.21 | 0.21 |
| Ex smoke. | 0.15 | 0.32 |
| Mild smoker | 0.24 | 0.19 |
| Moderate smoker | 0.23 | 0.22 |
| Heavy smoker | 0.34 | 0.18 |
| Comorbid | | |
| Allergic rhinitis | 0.28 | 0.54 |
| Sinusitis | 0.34 | 0.62 |
| Atopic dermatitis | 0.16 | 0.340 |
| Conjunctivitis | 0.26 | 0.32 |
| Obesity | 0.28 | 0.21 |
| Hypertension | 0.34 | 0.24 |
| Diabetes mellitus | 0.12 | 0.13 |
| Gastro esophageal reflux disease | 0.23 | 0.24 |

There is no significant correlation between side effect of Omalizumab treatment and (dose, frequency) of the drugs, smoking history and any comorbid condition like (allergic rhinitis, obesity, etc.).

There was no significant correlation between the side effects of Omalizumab treatment and the dose, the frequency of the drugs, smoking history and any comorbid condition like allergic rhinitis, obesity,…etc. (Table 4).

## Discussion

The long-term effectiveness of Omalizumab treatment of severe bronchial asthma was shown by the reduced frequency of asthma exacerbations, reduced hospital admission, the improvement in FEV1 values and the level of asthma control, as assessed by ACT scores, from six months to 3 years of treatment. Few data are available on long-term efficacy and safety of Omalizumab treatment in severe asthma [5,6]. Many studies reported that: insufficient adherence to Omalizumab treatment, varying from 40% to 70%, [7,8]. Insufficient efficacy has the main cause of discontinuation of Omalizumab treatment in life long studies [9]. Different studies have demonstrated that the dropout rate of treatment is higher in the first year [10,11]. This study aimed to assess the lifelong efficacy and safety of Omalizumab in patients with severe asthma.

In this study: Omalizumab has high efficacy on severe asthma course as moderate to severe exacerbations was prohibited, reduction in the annual exacerbation rate and hospitalizations [12]. In addition, the most excellent point of this study is the maximal efficacy present in the first 6 to12 months and the stability of these results till the end of the study [11] years, without loss of efficacy, this agreement with Cazzola *et al*., 2010 who concluded that the highest observed decline of acute exacerbation and hospitalization over the first 6 months was (90.5%) and over the first year was (96%) [13].

Omalizumab treatment has a significant dose reduction in corticosteroid (OCS and high dose of ICS) with maximal dose reduction and discontinuation present in the first year [14,15], but Tzortzaki *et al*. (2012) observed that the reductions of ICS dose started in the first year and reached the maximum dose reduction in the third year, 28% in the first year and 56% in the third year [16]. The discrepancy in the results may be due to differences in the demography of the patients.

Omalizumab therapy was associated with significant objective improvement in pulmonary functions (FEV1. FEV1/FVC, PEFR) especially in the first year [17] and sustained improvement from 4 to 10 years [16] even if patients have frequent acute exacerbation; Omalizumab treatment has a protective effect on lung function decline [18].

The values of total IgE showed a significant increase after the first six months of treatment, reached a peak in the first 12 months, and then it started to decrease,

with maximum decreasing level in the first two years. The initial increase in IgE explained by Omalizumab can detach IgE from FcεRI on the surface of basophils and mast cells [19]. The consequential reduction of the total IgE values decreased because of the binding of Omalizumab to serum IgE, so the free serum concentrations of the IgE decreased [20]. Additionally, Omalizumab inhibits the IgE production by preventing IgE interaction with receptors expressed by B-cells specialized in synthesizing IgE and it decreased the production of IL-4 from mast cells, the very important cytokine in the processing of IgE synthesis [21].

Regarding the safety of Omalizumab treatment, the most serious complications such as anaphylaxis and cancer were not present even in high doses of Omalizumab with high frequency and long duration (600 mg every other week for 7 to 10 years) suggesting that compliance is not related to the treatment schedule [22]. The most common complications were injection site reactions (70%), while headache, fever, nausea and myalgia were fewer complications, about 5% to 10% and more than 60% of those complications were present in the first year [23,24]. We would like to emphasize that local immediate reactions, would not lead to halting Omalizumab treatment [25]. The incidence of complications does not relate to the dose or frequency of the omalizumab, the smoking history of the patients or the presence of comorbid as (DM, HTN and obesity….) [26].

In that study, we found that; the persistent efficacy of Omalizumab treatments with an excellent safety profile was present even in a very long period of follow-up (10 years).

Limitations of the study: The first drawback is the lack of a control group. Another limitation is the number of the patients was small.

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**Conflicts of interest**

No conflict of interest.

**Authors' contributions**

HM: he wrote the manuscript. AE: she collected the data. NZ: she reviewed the manuscript. MH: he did analysis of the results. All authors have approved the manuscript.

**Abbreviations**

ACT, asthma control test;
DM, Diabetes mellitus; FceRI, high-affinity receptor;
FEV1, forced expiratory volume;
FVC, forced vital capacity;
HTN, hypertension;
ICS, inhaled corticosteroids;
IgE, immunoglobin E;
OCS, oral corticosteroids;
PEFR, peak expiratory flow rate.

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