ORIGINAL ARTICLE

Most common, real life factors affecting effectiveness of omalizumab asthma treatment: a 10-year study

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ABSTRACT

Aim To assess efficacy of omalizumab in moderate to severe asthma and notable factors affecting it, such as treatment compliance during the period of ten years. This retrospective, observational real life study is the first of this kind in the Gulf region and one of the worldwide rare long term omalizumab treatment studies.

Methods The treatment for 35 patients started in 2008. Twenty patients (ongoing group) proceeded with treatment and were assessed annually until 2017. Reasons for treatment discontinuation in 15 patients (drop-out group) were also assessed.

Results Before starting omalizumab the ongoing group of patients had history of ≥2 asthma exacerbations per year, which significantly decreased during the first year of the treatment ($p<0.001$), and for 14 (70%) patients ≤1 exacerbation stayed during the next 10 years. Since 2014 six (30%) patients had had ≥2 annual asthma exacerbations ($p<0.05$ in 2013; $p<0.05$ in 2014; $p<0.001$ in 2015; $p<0.01$ in 2016; $p<0.001$ in 2017). At the same time there was a significant drop in compliance index (CI) ($p<0.0001$).

Conclusion To our knowledge this is the first 10-year study of compliance and effectiveness, which may help finalize some practical suggestions to improve CI in clinical practice and to note acceptable variation in CI. It is important to recognize factors that can possibly affect effectiveness of the treatment and identify the patients who will have the best benefit from a long term omalizumab treatment.

Key words: omalizumab, compliance, efficacy, long term, efficacy

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INTRODUCTION

Over the past four decades, prevalence, morbidity and mortality of asthma have increased significantly (1, 2) and approximately 2-10% of patients with asthma have some form of "severe asthma", "uncontrolled asthma", "difficult-to-treat asthma" or "refractory asthma" (3). The prevalence of asthma in Kuwait was estimated to 15% for adults and 18% for children (4).

As there is no cure for asthma, the objective of the treatment is to control the clinical aspects of the disease (5). The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach to asthma control with the treatment being stepped up until control is achieved and maintained. For inadequately controlled asthma patients, that usually means adding oral corticosteroids (OCS) or anti immunoglobulin E (IgE) treatment (6). Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that inhibits the binding of IgE to high-affinity receptors (7). Omalizumab was first approved in 2003 to treat adults and children (12 ≥years of age) with moderate to severe persistent allergic asthma not controlled by inhaled corticosteroids (ICS), lately approved for children aged ≥6 years (8).

Based on current data it is still unclear when omalizumab treatment should be stopped (9). Omalizumab efficacy is usually evaluated at 16 weeks (10). However, in many patients an extension of the treatment for many years is essential to improve symptoms, medication use, lung function and quality of life outcomes. For this reason the assessment of omalizumab efficacy in real life settings during a prolonged period of time is in the focus (11,12).

The aim of our study was to assess efficacy of omalizumab and notable factors affecting it such as the treatment compliance during the period of ten years. Furthermore, this retrospective and observational real life study is the first of this kind in the Gulf region and one of the worldwide rare long term omalizumab treatment studies.

PATIENTS AND METHODS

Patients and study design

This real life, retrospective, observational study, assessed omalizumab effectiveness, in moderate to severe asthma patients, treatment compliance and factors that possibly affect those two over the period of 10 years. The study was conducted in Al Rashed Allergy Centre in Kuwait, which was the first Medical Institution allowed to apply it in medical treatment of uncontrolled, moderate to severe allergic bronchial asthma by the Ministry of Health in 2008.

The treatment for 35 patients started in 2008. Twenty patients (ongoing group) proceeded with the treatment and were assessed annually until 2017. Reasons for treatment discontinuation in 15 patients (drop out group) were also assessed.

Included patients had been diagnosed with moderate to severe allergic asthma with a poor response to maximal dose of inhaled corticosteroids with long acting beta 2 agonists (ICS\LABA). All patients fulfilled the following criteria: older than 12 years of age, total serum immunoglobulin E of 30-700 IU/ml, presence of atopy to inhalant allergens diagnosed by skin prick test (SPT), obstructive pattern by pulmonary function test, e. g. force expiratory volume in first second (FEV1) less than 80 %, with a bronchodilator response >12% and >200 mL, history of more than two asthma exacerbations per year (defined as emergency department/hospital admission or use of systemic corticosteroids). No female patient was pregnant or nursing at time of start with omalizumab treatment.

The Research Ethics Committee of the Ministry of Health of Kuwait approved this study and a signed informed consent was obtained from all study patients prior to start of omalizumab treatment.

Methods

Compliance to omalizumab (Compliance index, CI) was calculated comparing milligrams of a given dose of medication to milligrams of a presumed dose, per year. If CI ≤ 50% patient is defined as not compliant, if 50-75% poor compliance, if 76-89% good and if ≥ 90% high compliance to omalizumab treatment (13).

As factors possibly affecting asthma control, increase in body mass index (BMI), seasonal allergic rhinitis (SAR) and chronic rhino-sinusitis with nasal polyposis were also taken into consideration.

Omalizumab was administered every 2 or 4 weeks, subcutaneously, at the dose calculated taking into account the patients pre-treatment total IgE serum level and body weight. (14). During 10 years of omalizumab treatment, ICS/LABA dose was adjusted with stepping down or up again based on the control of asthma symptoms.

During the following 10 years, annual assessment of CI, number of asthma exacerbations (defined as a worsening of asthma requiring an emergency department/ hospital admission or systemic corticosteroid treatment) (15), FEV1, patient-reported outcomes from the asthma control test (ACT) (16), Mini Asthma Quality of Life Questionnaire (MiniAQLQ) (17) and global evaluation of treatment effectiveness (GETE) (18) were done for ongoing group. Data from patients' files (ACT, AQLQ, annual number of asthma exacerbations) were used to assess efficacy of omalizumab, which is defined with conclusive annual GETE assessment by a physician.

The ACT consists of five questions pertaining to the past 2-4 weeks. The brief questionnaire assesses asthma symptoms (daytime and nocturnal), use of rescue medication, and the effect of asthma on daily functioning. The total score was obtained by summing the scores for each item and ranges from 5 (poor control of asthma) to 25 (complete control of asthma). The minimally important difference of the ACT is 3 points or more (19).

The GETE Questionnaire represents a five-point scale: 1 - excellent (complete control of asthma), 2 - good (marked improvement), 3 - moderate (discernible, but limited improvement), 4 - poor (no appreciable change), and 5 – worsening. The Questionnaire was completed by physicians for every patient. The GETE 4 and 5 point corresponded to "lack of efficacy" and 1 and 2 point corresponded to "clinical efficacy" (20).

The MiniAQLQ contains 15 questions in the four domains. There are five items in the domain Symptoms, four items in the domain Activity Limitations, three items in the domain Emotional Function, and three items in the domain Environmental Stimuli. A change in score of greater than 0.5 was considered clinically important (21).

Statistical analysis

Non-parametric and parametric methods are used to calculate statistical significance. Kolmogorov-Smirnov test and Shapiro-Wilk test were used in order to test the normality of distribution of variables. Mean values were shown as arithmetic mean ± standard deviation in case of normal distribution of variables (age, body mass index and forced expiratory volume in first second) or median with minimum and maximum value inside brackets in the case of non-normal distribution (immunoglobulin E, doses of omalizumab per month, asthma control test, asthma quality of life questionnaire, number of exacerbations and compliance index). Student's t-test, Mann-Whitney test, Fisher's test and $\chi 2$ test were used for calculating the difference between the groups. ANOVA test was used to calculate the relative difference distribution variance between variables. The statistical hypotheses were tested at the level of $\alpha=0.05$, and the difference between the groups in the sample was considered significant when $p<0.05$ or less. Statistical significance was depicted as: $p<0.05$, $p<0.01$ and $p<0.001$.

RESULTS

During the year 2008, total of 35 patients with moderate to severe poorly control asthma on maximum ICS/LABA dose started with omalizumab as add on treatment. All patients fulfilled criteria for stepping up to omalizumab treatment by GINA guidelines at that time (26). Only one patient required daily use of oral corticosteroids prior omalizumab but stopped gradually after 6 months of omalizumab treatment.

Omalizumab was given to eight (22.86%) patients (five in ongoing group) every two weeks and to others every 4 weeks. No significant correlation was observed between monthly number of doses of omalizumab and compliance index in drop out ($p>0.05$; total Pearson coefficient of correlation $r=0.4141$; 95%CI: -0.1247 to 0.7643) nor in ongoing group ($p>0.05$; total Pearson coefficient of correlation $r=-0.383$; 95%CI: -0.7060 to 0.07173).

Until the assessment in 2017, 15 (42.8%) patients (11 females) had discontinued their further treatment for different reasons at different time points. The characteristics of ongoing and dropouts group are presented in Table 1.

The ongoing group was younger ($p<0.05$), but with similar distribution of gender, BMI, IgE and doses of omalizumab per month to later defined drop out group ($p>0.05$ for all measurements).

Table 1. Characteristics of the ongoing and dropout group before starting omalizumab

Characteristics	Ongoing group (n=20)	Drop out group (n=15)	p
Age (years) (mean±SD)	41.4 ± 8.95	51.87 ± 16.37	0.021*
Females (no; %)	15 (75.0)	11 (73.3)	0.7802
Body Mass Index (kg/m2) (mean±SD)	30.13 ± 6.78	30.58 ± 4.29	0.8224
Immunoglobulin E (IU/mL) (median) (minimum; maximum)	125 (65; 223)	279 (55; 576)	0.523
Doses of omalizumab per month (median) (minimum; maximum)	1 (1, 2)	1 (1; 2)	0.6171
Forced Expiratory Volume in First Second (% of predicted value) (mean±SD)	77.3±14.5	69.7±13.6	0.05*

* significant difference

Increased BMI, as comorbidity before starting Omalizumab, was noted in 13 (37.14%) patients (10 from the ongoing group and 3 in the drop-out group). The BMI was not assessed in drop-out group because of a shorter follow up period.

Skin prick test (SPT) results in all patients before starting omalizumab showed a domination of sensitisation to perennial (*Dermatophagoides pteronisinus*, *Dermatophagoides farinei*, *Cat dander, Alternaria alternata* spp.) or both perennial and seasonal (*Salsola kali, Bermuda grass*) allergens. The SPT positive for only seasonal allergens was found in eight (22.86%) patients (five in the drop-out group).

Before starting omalizumab all patients in ongoing group (n=20) had history of two or more asthma exacerbations per year, which significantly decreased during the first year of treatment ($p<0.001$) and for 11 (55%) patients one exacerbation remained during next 10 years.

The FEV1, ACT and AQLQ improved significantly during 10 years on omalizumab (baseline vs after 10 years: FEV**1** % of predicted value (mimum; maximum): 68.5 (21; 94) vs 72.5 (38; 106) ($p<0.01$); ACT median (mimum; maximum): 15.5 (8; 21 vs 21 (12; 25) ($p<0.0001$); AQLQ median (mimum; maximum): 30 (15; 60 vs 77 (31; 87 ($p<0.0001$). Actually, FEV1 improved significantly after one year of treatment ($p<0.001$) and remained similar during next 9 years. Also, ACT improved significantly after one year (2008 vs 2009 $p<0.0001$), but showed additional improvement after 2 years of treatment (2009 vs 2010 $p<0.01$) and then remained similar during next 8 years (Table 2).

Over ten years, beside 10 (50.0%) patients with high BMI from the baseline, three (15.0%) experienced increase in BMI. Out of four (20.0%) patients that notably reduced BMI over ten years, two (10.0%) experienced increase in the number of asthma exacerbations (after 6th year of omalizumab treatment).

Table 2. Parameters assessed before (baseline) and after 10 years of omalizumab for ongoing group

Parameter	Baseline	After 10 years	p
Body Mass Index (kg/m2) (mean±SD)	30.13 ± 6.78	31.32 ± 4.05	0.1115
Forced Expiratory Volume in First Second (% predicted value) (minimum; maximum)	68.5 (21; 94)	72.5 (38; 106)	0.0086*
Asthma Control Test (median) (minimum and maximum)	15.5 (8; 21)	21 (12; 25)	<0.0001*
Change in Asthma Control Test >3 (no, %)	-	14 (70.0%)	-
Asthma Quality of Life Questionnaire (median) (minimum and maximum)	30 (15; 60)	77 (31; 87)	<0.0001*
Change in Asthma Quality of Life Questionnaire >0.5 (no, %)		20 (100)	-

* significant difference

In the drop-out group mean duration of omalizumab treatment was 3±1.65 years, which was discontinued in 8 (22.8%) patients after 2 years. In this group seven (20.0%) patients were discontinued from the treatment due to reasons unrelated to the effectiveness of the treatment (adverse events or new comorbidities). Eight out of 15 (53.33%) patients stopped taking omalizumab due to very poor (n=5) or excellent (n=3) response based on GETE (Table 3).

Table 3. Drop out according to years of treatment

Drop-out according to treatment years	Number (%) of patients in drop out group
after 1 year	1 (2.8)
after 2 years	7 (20.0)
after 3 years	3 (8.5)
after 4 years	1 (2.8)
after 6 years	3 (8.5)

For the ongoing group the number of asthma exacerbations significantly dropped during the first year on omalizumab and it was ≤1 during the first 6 years of the treatment (from 2008 to 2013). From the year 2014, six (out of 20 patients) (30.0%) had ≥2 annual asthma exacerbations ($p<0.05$ in 2013; $p<0.05$ in 2014; $p<0.001$ in 2015; $p<0.01$ in 2016; $p<0.001$ in 2017). At the same time there was a significant drop in CI ($p<0.0001$) (Table 4).

During the period of ten years CI was similar among all 20 patients ($p>0.05$ for all measurements) except

in 2015, when six patients with ≥2 exacerbations in 2014 had higher CI than other patients ($p<0.05$). An increase in CI did not affect annual trend in asthma exacerbations, which remains the same or increased in five of six patients (83.33%).

Average CI in ongoing and drop-out group was similar ($p>0.05$) (Table 4).

Table 4. Number of asthma exacerbations and Compliance Index for ongoing group (n=20)

Year	Number of Exacerbations (median) (minimum; maximum)	Compliance Index (median) (minimum; maximum)
2008	0 (0; 1)	1 (0.7; 1)
2009	0 (0; 1)	1 (0; 1)
2010	0 (0; 1)	1 (0; 3)
2011	0 (0; 0)	0.9 (0; 1)
2012	0 (0; 1)	0.9 (0; 1)
2013	0 (0; 1)	0.8 (0; 1)
2014	0 (0; 2)	0.8 (0.5; 0.9)
2015	0 (0; 3)	0.8 (0.2; 1)
2016	0 (0; 4)	0.8 (0.3; 1)
2017	0.5 (0; 4)	0.8 (0.4; 0.9)
p	<0.0001	<0.0001

There was no significant correlation in monthly doses of omalizumab (every 2 weeks vs. every 4 weeks) and average CI between six patients with an increase in asthma exacerbations and other 14 patients ($p>0.05$; patients with ≥2 exacerbations: total Pearson coefficient of correlation r=-0.5356; 95%CI: -0.8850-0.1996; patients with ≤1 exacerbations: total Pearson coefficient of correlation r=-0.2348; 95%CI: -0.7317-0.4250) (Table 4).

In the ongoing group during assessment in 2017, 14 (70%) patients were defined as excellent to good and six (30%) as good to moderate treatment responders (defined by GETE physician assessment).

DISCUSION

Although omalizumab is an effective add-on therapy of uncontrolled moderate to severe persistent allergic asthma, most studies discussed its efficacy through relatively short period of time (i.e. ≤4 years) (22), with the exceptions of a few reports, which proved favourable outcome beyond 4 years of treatment (23,24). A recent study following eight patients up to nine years documented that long-term treatment with omalizumab was associated with continued benefits in reducing symptoms, exacerbations and medication burden without any safety concerns (12). Our overall results also support favourable outcome with excellent to good asthma control in 70% of patients over 10 years. A proportion of patients who discontinued omalizumab treatment due to lack of efficacy was significantly higher in real-life studies than in randomized clinical trials (25). Perhaps strict inclusion and exclusion criteria in randomized clinical trials could alter omalizumab effectiveness in comparison to the real-life settings.

In our study, 42.8% patients dropped out the treatment mostly due to lack of efficacy (after 2 years) or newly diagnosed comorbidities (during 6 years).

Response to omalizumab was routinely assessed after 16 weeks of therapy (26) but late responders could benefit from longer period of assessment (27).

After 2 years on omalizumab 14.28% of patients did not show any significant improvement of FEV1, ACT, or annual number of asthma exacerbations in our study. Due to mild improvement in AQOL they decided to continue with the treatment despite overall CI <60%. Disregarding physician's advice these patients have also shown very poor compliance with standard asthma treatment and follow up visits since they stopped with omalizumab. During the same period of 2 years 8.57% of patients had excellent response with high CI, and were advised to stop omalizumab for observational time. Their asthma remained very well controlled with standard asthma treatment (step 4 and step 3 GINA). It seems that a small fraction of patients could be profiled as eligible or ineligible for a long-term treatment during the period of ≤2 years based on effectiveness and compliance.

Clinical benefits and effectiveness of omalizumab were mostly seen in reduction of asthma exacerbations and ICS dose (28), as well as in improvement of AQOL (29) or FEV1 (30). In this study majority of patients had improvement in FEV1, ACT, AQOL and reduction in asthma exacerbations after the first year on omalizumab. Similar results were documented in our previous 4-year study (11).

Due to different parameters used to assess omalizumab efficacy and controversial data of some studies (31) good predicting markers of omalizumab treatment are still missing (32). Improvement in asthma control with omalizumab led to the reduction of concomitant medication use (33) and in our study 57.14% of patients were stepped down from the maximum dose of ICS/LABA

during the first five years of treatment. However, 30% patients, who were defined during the five-year treatment as good to excellent responders to omalizumab, experienced ≥2 exacerbations of asthma in the sixth year due to which they were stepped up back to the maximum dose of ICS\LABA; other 70% patients, who were also defined as excellent to good responders, remained like that during all 10 years.

Due to the decrease in asthma control in a relatively high number of patients (30%) we assessed CI, changes in BMI, presence of seasonal allergies and chronic rhinosinusitis with nasal polyposis as possible factors affecting omalizumab efficacy and compliance. For the evaluation of compliance many methods are currently available but none of them could be considered as the gold standard (34). Some studies reported that about 50% of asthma patients are not compliant with the given treatment (35) and CI greater than 80% has been considered as satisfactory (36). One study reported that higher compliance did not correspond to high response rate (13). In our study CI decreased from high to good in all patients over 10 years. We noticed the first mild decrease in CI during the fifth year of the treatment, but in 70% patients CI decrease did not affect asthma control. On the other side, there was no improvement in asthma control for 30% of patients who increased CI after the initial drop. It seems that CI from 0.8-1 presented an acceptable range for asthma control in majority of our patients.

Although in Jason et al. study 4-week dosing regimen achieved better compliance than 2-week regimen (37), in our study there was no significant difference in CI between 2- and 4-week regimens. There was also no effect of dosing regimen on CI among 30% of patients with decreased asthma control.

Caminati et al. highlighted that sensitization to a perennial allergen was missing in more than 20% of patients undergoing omalizumab treatment (25) despite being included in the prescription criteria (14). Domingo et al. proved that omalizumab offered the same clinical benefits regardless of whether asthma was caused by a seasonal or a perennial allergen (38).

In our study 15.0% ongoing group patients had SPT positive only for seasonal allergens (*Salsola kali* and *Bermuda* grass, which are most common inhalant allergens in Kuwait), but also history of chronic rhinosinusitis (CRS) with nasal polyposis and they were among 30% of patients who experienced decreased asthma control. Asthmatic patients with CRS and nasal polyposis had more poorly controlled asthma, increased airway obstruction and marked lower airway inflammation (39). Omalizumab reduces the size of nasal polyps and improves the quality of life (40) improving nasal outcomes (symptoms, nasal endoscopy and computed tomography results), but it does not improve pulmonary outcomes (symptoms and pulmonary function test results) (41). In our study 30.0% patients had CRS with nasal polyposis from which 66.67% experienced ≥ 2 asthma exacerbations after 5 years being fully controlled on omalizumab. These patients were regularly followed by otolaryngologist. Chronic rhinosinusitis without polyposis was found in 20% patients with excellent response to omalizumab. These data point out complexity and dynamics of asthma control in patients with CRS with nasal polyposis and demand closer follow up of these patients.

We would like to point out a loss of bronchodilator response in one female patient, with spirometry showing dominantly restrictive pattern, after 8 years on omalizumab without any significant changes on her computed tomography (CT) chest. This is opposite to the studies proving that omalizumab decreased airway remodelling in patients with severe asthma (42).

Interestingly, 40-year-old female patient, without comorbidities, with excellent asthma control and good CI, but who had stopped omalizumab due to two pregnancies during the first 5 years and then continued the treatment without significant deterioration in symptoms, lost asthma control (≥2 asthma exacerbations annually) during the sixth year on omalizumab.

Molimar et al. noted that 20% of previous responders failed to respond to the reintroduction of omalizumab (43), but Busse et al. reported that 60% of patients remained free of asthma exacerbations at one year after discontinuation of long-term omalizumab (≥5 years) (44). The question is whether there is a possible late effect of repeated long term treatment discontinuation (app. one year) on effectiveness and this requires closer monitoring of similar cases.

In conclusion, according to our knowledge this is the first 10-year study of compliance and effectiveness, which may help finalize some practical suggestions to improve compliance in routine clinical practice and to note acceptable variation in compliance index. It is important to recognize factors that can possibly affect effectiveness of the treatment and identify the patients who will have the best benefit from long-term omalizumab treatment.

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