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Tolerability of Omalizumab in Asthma as a Major Compliance Factor: 10-Year Follow Up

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Abstract

BACKGROUND: There is a lack of data related to real life, long-term safety, tolerability and compliance of omalizumab treatment in asthma patients beyond 6 years.

AIM: Study aimed to assess safety, tolerability, compliance and all reasons for treatment discontinuation during 10 years on omalizumab.

SUBJECT AND METHODS: This is a retrospective, observational study of uncontrolled asthma patients receiving omalizumab for the last 10 years. All data were collected from patients' files (demographics, adverse events, comorbidities, compliance index, reasons for discontinuation of omalizumab). Reactions to omalizumab were classified as local and systemic, and their severity as mild, moderate or severe. Reactions were either immediate (minutes to hours after drug administration) or delayed (after days). Compliance to omalizumab, defined as Compliance index (CI), was calculated by comparing milligrams of given to milligrams of prescribed dose/ per year.

RESULTS: Out of 35 patients receiving omalizumab, 15 drop out at different time points mostly due to treatment efficacy or appearance of new comorbidities. Patients who continue for the next ten years had mild to moderate adverse events related to omalizumab. There was no increased risk of severe adverse events during 10 years on omalizumab. Patient's treatment tolerability, despite mild to moderate adverse events, is in favour of compliance.

CONCLUSION: Compliance with omalizumab mildly decreased over 10 years but was not affected by severe adverse events of treatment or new comorbidities. Although, omalizumab is safe medicine appearance of new comorbidities has to be closely followed up.

Introduction

Asthma is a common, chronic respiratory disease affecting 15% of adults and 18% of children in Kuwait [1]. Worldwide, approximately 20% of asthma patients have severe asthma, of which 20% is inadequately controlled [2]. The Global Initiative for Asthma (GINA) guidelines recommends a stepwise treatment until control is achieved and maintained. GINA recommends adding oral corticosteroids (OCS) or anti-Immunoglobulin E (IgE) treatment with omalizumab in uncontrolled asthma patients [3]. Due to well-known severe side effects of oral corticosteroids, omalizumab represented promising, safer, approach to difficult to control allergic asthma [4].

Omalizumab was first approved in 2003 to treat adults and children 12 years of age and older with moderate to severe persistent allergic asthma not controlled by inhaled corticosteroids (ICS) and is approved lately for children aged ≥ 6 years [5].

Based on current data it is still unclear when omalizumab treatment should be stopped after asthma control is achieved [6]. This statement raised many issues regarding the long-term safety, tolerability, compliance, and possible correlation of same during omalizumab treatment.

There are noted side effects of omalizumab recognised by the manufacturer [7] or FDA (The Food and Drug Administration) [8]. However, omalizumab was found to be in general a well-tolerated therapy with frequency and severity of adverse events (AE) similar to patients receiving placebo or best available

therapy [9]. The study aimed to assess safety, tolerability, compliance and all reasons for treatment discontinuation during 10 years on omalizumab.

Patients and Methods

This was real life, retrospective, observational study, conducted at Al Rashed Allergy Centre, the first Medical Institution that applied omalizumab for uncontrolled, moderate to severe allergic Asthma, since 2008 in Kuwait. Inclusion and exclusion criteria applied for 35 patients after treatment is stepped up on level 5 GINA [10]. All data were collected from patients' files. Patients who stopped with omalizumab for different reasons at different time points till the last assessment in 2017, were defined as drop out (15 patients) and a patient who continued (20 patients) as an ongoing group. Details of any adverse events (whether reported or not in literature) occurred during treatment were recorded, as well as details of any newly diagnosed comorbidities. Omalizumab was administered every 2 or 4 weeks, subcutaneously, at the dose calculated based on patients pre-treatment total IgE serum level and body weight [11]. Adverse events to omalizumab were classified as systemic and local reactions, and their severity was classified by both physician and patient (mild, moderate, severe) to assess eligibility for continuation of treatment. Reactions were divided into immediate (few minutes to hours after administration drug) and delayed (after days). Compliance to omalizumab (Compliance index-CI) was calculated by comparing milligrams of given dose to milligrams of prescribed dose/per year and defined as CI ≤ 50% not compliant, 50-75% poor, 76-89% good and ≥ 90% as high compliance [12].

Results

A total of 35 patients started omalizumab during 2008. All patients fulfilled GINA stepping up criteria [13]. Only one patient required daily use of oral corticosteroids prior omalizumab but stopped gradually after 6 months of treatment. Thirteen patients were receiving omalizumab every 2 while resting every 4 weeks. Till assessment in 2017, 15 patients (11 females) discontinued treatment for different reasons at different time points. Demographic data of drop out and ongoing treatment group (20 patients) are presented in Table 1.

The ongoing group was younger ($p < 0.05$), while gender, BMI and monthly doses of omalizumab showed the similar distribution in both groups ($p > 0.05$).

Table 1: Characteristics of patients in ongoing and dropouts group

	On going N = 20	Drop outs N = 15	p value
Age* in years, mean±SD	41.4 ± 8.95	51.87 ± 16.37	0.0210**
Female (n; %)	15 (75.0%)	11 (73.3%)	0.7802
BMI*	30.13 ± 6.78	30.58 ± 4.29	0.8224
Duration of treatment in years, mean±SD			
-Any reason	-	3 ± 1,65	ND
-Treatment-related AE	-	4	
Comorbidities at baseline (n, %)			
Nasal polyps	9 (45.0%)	0 (0.0%)	0.0043**
Diabetes mellitus type 2	3 (15.0%)	2 (13.3%)	1.000
Hypertension	3 (15.0%)	0 (0.0%)	0.24
Gastroesophageal reflux disease	6 (30.0%)	2 (13.3%)	0.42
Chronis rhinosinusitis	4 (20.0%)	3 (20.0%)	1.00
Seasonal allergic rhinitis	2 (10.0%)	1 (6.67%)	1.00
Hypothyroidism	3 (15.0%)	1 (6.67%)	0.62
Eczema	1 (5.0%)	0 (0.0%)	1.00
Osteoporosis	4 (20.0%)	1 (6.67%)	0.36
Psoriasis	1 (5.0%)	0 (0.0%)	1.00
Obesity (BMI≥30 kg/m^2)	10 (50.0%)	6 (40.0%)	0.29
Comorbidities diagnosed during treatment (n, %)			
Diabetes mellitus type 2	2 (10.0%)	0 (0.0%)	0.5
Hypertension	2 (10.0%)	0 (0.0%)	0.5
Psoriasis	1 (5.0%)	1 (6.67%)	1.00
Obesity (BMI≥30 kg/m^2)	3 (15.0%)	0 (0.0%)	0.24
Thyroiditis	1 (5.0%)	0 (0.0%)	1.00
Gastroesophageal reflux disease	1 (5.0%)	0 (0.0%)	1.00
Ischaemic heart disease	1 (5.0%)	0 (0.0%)	1.00
Megaloblastic anaemia	2 (10.0%)	0 (0.0%)	0.5
Alzheimer disease	0 (0.0%)	1 (6.67%)	0.429
Cervical tuberculose adenitis	0 (0.0%)	1 (6.67%)	0.43
Liver cirrhosis	0 (0.0%)	1 (6.67%)	0.43
Hypogonadism	0 (0.0%)	1 (6.67%)	0.43

Index: BMI-body mass index; SD-standard deviation; AE-adverse events; ND-not did; (*)-Mean age and BMI before the start of omalizumab; (**)-difference was significant.

Among an equal number of presented comorbidities in both groups ($p > 0.05$), nasal polyposis was more frequent in the ongoing group ($p < 0.01$), number of new comorbidities diagnosed while on omalizumab were similarly noticed in both groups ($p > 0.05$).

Anaphylaxis related to omalizumab has been described as a combination of any of the following: angioedema of the throat or tongue, bronchospasm, hypotension, syncope, and urticaria [14] which defines severe, systemic, treatment stopping reaction.

On treatment with omalizumab, no immediate systemic reaction (anaphylaxis or generalised urticaria) was observed in our patients at the beginning or during the next ten years. From 35 patients, 6 had mild to moderate local, and 6 had a moderate systemic reaction during the first week after omalizumab injection, and all of them continue treatment for the next 10 years (Table 2).

The majority of patients reported adverse events from the start of omalizumab while others after more than 5 years (e.g. back pain), and few patients had occasional (> 3 times per year) occurrence of symptoms. All patients who reported any of these side effects were evaluated fully for organic and non-organic causes of symptoms. However, no cause was found.

One 33-year-old female patient stopped omalizumab after 4 years (CI = 75%) due to pain in the arms and legs up to 5 days after each injection, and this has been increasing in intensity with years of treatment.

Table 2: Treatment-related and other adverse events (AE) in patients on omalizumab

	Patients N = 35 (100%)
Discontinuation for any reason	15 (42.8%)
Treatment related AEs	12 (34.3%)
Immediate systemic reaction	0 (0%)
Immediate local reaction	6 (17.1%)
Patient with AE non-causing discontinuation	12 (34.3%)
Other than treatment-related AEs causing discontinuation	
a) poor or very good response on Omalizumab	8 (22.8%)
b) Psoriasis, newly diagnosed	1 (2.8%)
c) Alzheimer disease	1 (2.8%)
d) Liver cirrhosis	1 (2.8%)
e) Cervical tuberculose adenitis	1 (2.8%)
f) Hypogonadism	1 (2.8%)
g) Death during an asthma attack	1 (2.8%)
Type of treatment-related AE causing discontinuation	
a) pain in arms and legs	1 (2.8%)
Type of AE non causing discontinuation	
a) pain at the site of injection	5 (14.3%)
b) pain in arms and legs	1 (2.8%)
c) pain in legs	2 (5.1%)
d) back pain	3 (8.6%)
e) nervousness, fatigue and insomnia	6 (17.1%)
f) swelling at the site of injection	2 (5.1%)
g) subjectively perceived increase in hair loss	6 (17.1%)
h) venous thromalizumabosis	1 (2.8%)
Dropouts according to treatment years	
a) after 1 year	1 (2.8%)
b) after 2 years	7 (20%)
c) after 3 years	3 (8.5%)
d) after 4 years	1 (2.8%)
e) after 6 years	3 (8.5%)

Other 14 patients stopped omalizumab due to other than treatment-related adverse events. Reason for discontinuation of omalizumab by a physician, for five patients after 2 years, was poor compliance and poor effectiveness estimated by asthma control parameters [15]. During the first 3 years of treatment, three patients showed significant clinical improvement and subjectively felt very well, so they decided to stop omalizumab. In 5 from 15 patients reason for omalizumab discontinuation was the appearance of new comorbidity and one female patient died during severe asthma attack during the second year on omalizumab (deep depressive state after a family tragedy, history of near-fatal asthma attacks, CI = 60%).

Median CI for drop out group was 72% for all years on omalizumab, and for ongoing group significantly decreased over 10 years to 80% (Table 3). Annual Compliance index was higher in period from 2008 till 2012, compared to 2013 till 2017 ($p < 0.05$, $p < 0.0001$, $p < 0.05$, $p < 0.001$ and $p < 0.0001$). There is no significant difference in CI between patients with and without AE in ongoing group ($p > 0.05$).

Table 3: Annual Compliance Index for the ongoing group (n = 20)

Year	Compliance index
2008.	1
2009.	1
2010.	1
2011.	0.9
2012.	0.9
2013.	0.8
2014.	0.8
2015.	0.8
2016.	0.8
2017.	0.8
p-value	< 0.0001*

*difference was significant.

Discussion

If omalizumab considers years-long treatment for moderate to severe uncontrolled asthma, there are some concerns regarding tolerability that requires close follow up.

As concluded by Di Bona et al., long-term treatment with omalizumab appears remarkably safe and well tolerated in a real-life setting. Prolonged omalizumab treatment for many consecutive years did not increase the risk of side effects, particularly anaphylaxis [16]. Data from Randomized Controlled Trials (RTC) and post-marketing surveillance showed that hypersensitivity reaction to omalizumab are not that frequent and anaphylaxis is rare, occurring in about 0.09% of patients [17]. Safety data from real life observational studies are consistent with the results of RCT mostly for short-term studies [18]. Based on our data, even the 10-year long treatment with omalizumab does not increase the rate of anaphylaxis. These results confirm that omalizumab has a good safety profile, both in the experimental and real-life setting [19].

Three studies reported adverse events as the main cause of treatment discontinuation, without any significant differences regarding drop-out rate [20] [21] [22].

Only one female patient in our study stopped omalizumab due to increased, post injection pain in arms and legs, lasting up to 5 days. She was satisfied with the effectiveness of treatment and tolerated pain for 4 years with CI 75%.

This finding suggests that tolerability is an important issue and consequently it has to be carefully considered; as evidenced with other treatments, it can significantly affect compliance [23]. Most observational studies reported a low discontinuation rate due to AE over a mean treatment period of 1-2 years [24] [25] [26] [27] [28] [29] [30], same applied for period of 3 and 4 years respectively [31] [32] and 9 years study reported a 6.6% drop out over a mean treatment period of 3.8 years [16]. In our study, local reaction at the injection site was the commonest adverse event. Pain in arms and legs or legs only reported 7.9 % (3 out of 35 patients) and immediate local reactions (pain/swelling at the site of injection) 17.1% patients, but that was not reason enough to stop with the treatment during the next 10 years. Di Bona et al. reported only one patient with immediate local reaction (injection site swelling) [16]. Subjectively perceived increase in hair loss in 17.1% of our patients is also recognised in different reports [33], but it has to be properly assessed and evaluated to be labelled as omalizumab induced. Nervousness, fatigue and insomnia are reported by 17.1% of patients in our study. There is no data about nervousness and its correlation with asthma or asthma treatment. It is known that chronic diseases

such as asthma can cause depression [34]. Fatigue and insomnia can be part of depression symptoms spectrum [35]. Fatigue and insomnia are also reported as mild side effects of omalizumab, and our patients reported that it lasted 2 days after injection [36].

In real-life studies, the drop-out rate ranged from 0 to 45.5 %, and in most cases, lack of efficacy was responsible for treatment discontinuation [37].

Majority of our patients (n = 8) who stopped with omalizumab did so because of the poor or excellent effect of treatment after the first 2 years, and the others due to newly diagnosed comorbidities. In individuals with severe asthma, comorbidities are common, with the most prevalent being gastroesophageal reflux disease (GERD), sinusitis, allergic rhinitis and nasal polyposis [38]. Same comorbidities were present in our patients before the start of omalizumab, but they didn't affect later treatment tolerability and compliance. Although there is no confirmed correlation with omalizumab treatment, it's notable that 5 patients in drop out group developed new comorbidities over the years on omalizumab. A 70-year-old female patient, otherwise healthy, stopped omalizumab when diagnosed with Alzheimer disease during the sixth year on treatment (CI = 90%). There is no data about Alzheimer disease in patients on omalizumab, but there are data about the increased incidence of Alzheimer in Arab countries [39]. A 73-year-old male patient, who had no history of smoking, alcohol intake or chronic disease, developed liver cirrhosis in full clinical feature during the 6th year on omalizumab (CI = 75%) and died few months after diagnosis. Male patient (38-year-old) with mild improvement on omalizumab stopped the treatment when diagnosed with hypogonadism during the first year of treatment (CI = 80%), and one female patient (39-year-old) was diagnosed with thyroiditis (normal hormonal status) after 7 years on omalizumab, and she continues with omalizumab treatment. We couldn't find any published reports of the liver, thyroid or gonadal hormones issue in omalizumab patients. A 34 year old female decided to stop omalizumab after 2 years (CI = 90%) when diagnosed with cervical tuberculous adenitis.

There are no studies supporting the correlation between omalizumab and tuberculosis, but an extra-pulmonary tuberculosis infection rate of 30% in Saudi Arabia remains above the global rate [40]. Regarding infectious disease, the only low risk of parasitic infestation while on omalizumab is reported by a specific study carried out in Brazil [41]. A male (53 years old) patient stoped omalizumab when diagnosed with psoriasis during the first year of treatment (CI = 90%). After 7 years of omalizumab one (51-year-old), the female patient is also diagnosed with psoriasis and continue with treatment. Al-Mazeedi et al. conducted a descriptive study to determine the extent of psoriasis in Kuwait and the risk factors associated with it. The incidence and prevalence of psoriasis in Kuwait were calculated to be 0.11% and 0.45%, respectively and usual age of onset is between 15 and 30 years, although it can present at any age [42]. The appearance of psoriasis doesn't seem to be affected by omalizumab or even treatment duration.

Newly diagnosed comorbidities in the ongoing group seem not to affect tolerability and compliance. We noted 2 patients with newly diagnosed type 2 diabetes mellitus (after 8 years on omalizumab, older than 60 year of age with positive family history for diabetes mellitus), two cases of hypertension (patients with positive family history for hypertension, both older than 60 year), and one gastroesophageal reflux disease-GERD (after 4 years of omalizumab treatment, history of treated Helicobacter pylori infection). In our study, one female patient has ischemic heart disease-IHD (49-year-old, history of hypertension and transient ischemic brain attack - TIA, after 3 years on omalizumab). Although EXCELS study's interim safety data showed an excess of cardiovascular and cerebrovascular events in the patients on omalizumab compared with the asthma control group [8] [43], FDA did not recommend any changes to the prescribing information (i.e., package insert) but did recommend increased awareness [44]. There is a question of possible adjustment for asthma treatment, omalizumab dosing and parameters for follow up, for these high-risk patients.

In our study, there is also, no newly diagnosed malignancies over the 10 year which is also consistent with EXCEL study [45].

Two patients had megaloblastic anaemia (females, after 6 years on omalizumab) and one (female, 46-year-old, after 9 years on omalizumab) had elevated specific liver enzymes with negative assessment for infective, autoimmune and malignant diseases.

For noted comorbidities, the bigger cohort with long-term follows up is needed, with a closer observation on all details that can help in selecting patients for omalizumab. Some studies reported that about 50% of asthma patients are not compliant with the given treatment. The issue becomes even more relevant in specific age groups such as children, adolescent and elderly [46]. A univocal and standardised tool for evaluation of adherence is lacking [47]. Another controversial aspect concerns the definition of "acceptable adherence". In some large studies, an adherence rate greater than 80 % has been considered satisfactory, but a consensus about this issue has not been reached. Patients requiring treatment with injected drugs, like omalizumab, are more easily monitored, as treatment administration requires medical supervision [48]. Treatment discontinuation can be easily detected and considered as a consistent marker of compliance.

Harjinder et al., the study reported that visit compliance does not statistically impact the response rate to omalizumab and higher compliance does not

correspond to the high response rate [12]. In our study, there is a significant decrease in compliance expressed as drop-in compliance index from high to good for 10 years. In an ongoing group, 12 patients had mild to moderate adverse events that should be noted as possible reasons for compliance decrease. Although there is no significant difference in CI between patients with or without reported AE in an ongoing group. Efficacy seems to be a more significant factor affecting omalizumab treatment discontinuation than, other than severe, AE of the same medicine. Tolerability of mild to moderate AE in favour of treatment efficacy points out an acceptable range of CI from 76% and more.

That emphasises better patient selection and devoted follow up by medical stuff during treatment of moderate to severe uncontrolled Bronchial Asthma. More tool is still required to lead physician, and patient as well, from the predicted effect of omalizumab to real beneficial one.

As limitation of our work it can be noted that in real-life observational studies is difficult to avoid or properly assess bias and conclusions are not easily applicable across a generalised population. Furthermore, often only a descriptive analysis has been provided.

Nevertheless, to our knowledge, this is first 10 years study of tolerability, safety and compliance which may help in finalising some practical suggestions to improve compliance in routine clinical practice.

In conclusion, the most important benefit of our study is a long observational period for omalizumab treatment. Our results indicate that the drug can be administered for many years without increased risk of severe adverse events. Continuation of treatment despite mild to moderate adverse events is due to the patient's perception of omalizumab effectiveness. Therefore, clinicians should discuss tolerability issues with their patients as part of a strategy aiming at improving compliance. To our knowledge, newly diagnosed conditions such as liver cirrhosis, thyroiditis and megaloblastic anaemia documented after more than 6 years of treatment in our patients, are not described in available studies and demand closer further observation regarding the possible causative role of omalizumab.

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