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ORIGINAL ARTICLE

Treating severe Ig-E mediated Allergic Adult Asthmatics with Omalizumab outside the dosing table

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Introduction: According to the summary of product characteristics of omalizumab, patients whose weight and/or total IgE falls outside the dosing table are not eligible to receive omalizumab. In view of the absence of alternative biological agents for asthma in Malta at time of data collection, it was decided that such patients would receive the maximum recommended dose of 600mg every 2 weeks.

Methods: The aim of this study was to assess the safety, efficacy and tolerability of adult patients receiving omalizumab for asthma who did not fall within the dosing table and compare these factors to patients within the dosing table. All adult patients receiving omalizumab for more than one year were recruited. Data collection included demographic data, baseline weight, IgE levels, side-effects reported, number of exacerbations, hospitalizations and corticosteroids needed.

Results: Our cohort included 71 patients (mean age 48.8 ± 13.3, 45% males). When comparing patients who received omalizumab according to the recommended dosing chart (n=56) versus those who did not (n=15), there was no statistical significance for treatment discontinuation (p=0.79). Mean baseline IgE was higher in the outside of dosing category (p=0.001). Mean total number of exacerbations since treatment initiation was significantly less for the outside of dosing category (p=0.01) as was the mean total number of systemic corticosteroid courses (p=0.02). There was no statistical significance in hospitalization rate (p=0.09).

Conclusions: Our results reaffirm our decision to treat severe IgE-mediated asthmatic patients with an IgE level and/or weight outside the dosing chart with the maximum recommended dose with good clinical outcomes and good safety and tolerability profiles.

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Omalizumab is a recombinant DNA-derived humanized IgG1 monoclonal antibody that selectively binds to free and membrane-bound immunoglobulin E (IgE) antibodies. It is the first biologic to have been approved internationally and is currently used globally for severe allergic asthma. It is indicated as an add-on therapy in patients with severe persistent allergic asthma who have positive reactivity to a perennial aero-allergen, elevated IgE level, reduced lung function and symptoms consistent with poor asthma control despite maximal treatment.[1,2]

Dosing of omalizumab is calculated according to dose determination charts and is administered every 2 or 4 weeks depending on a patient's baseline IgE level and the patient's weight. According to the Summary of Products Characteristics (SPC) for omalizumab, the maximum recommended dose is 600mg every two weeks. If a patient's IgE level or body weight is outside the limits of the dosing table, omalizumab should not be prescribed.[3]

In view of the absence of availability of alternative biological agents for severe allergic asthma at our local hospital, it was decided that our patients in whom omalizumab was clinically indicated but fell outside the dosing table in view of the patient's elevated body weight and/or IgE level, and hence not eligible to receive the medication, they would still receive the maximal dose of 600mg every 2 weeks.

The aim of this study was to assess the safety, efficacy and tolerability of adult patients receiving omalizumab for severe allergic asthma who did not fall within the recommended dosing regime. The aim was to compare these factors to patients receiving omalizumab within the dosing table.

Our intention was not to compare participants asthma status pre- omalizumab treatment to their current status post- treatment, since patients that need biological therapy such as omalizumab already indicates that they have poor asthma control with recurrent exacerbations needing systemic corticosteroids and/or hospital admissions, on full maximal inhaler treatment with high dose inhaled corticosteroids and long-acting beta-2-agonists, +/- leukotriene receptor antagonists, and long-acting muscarinic antagonists as per the Global Initiative for Asthma (GINA) guidelines.[4]

MATERIAL AND METHODS

Omalizumab was approved and made available in Malta in 2012. Dosing of omalizumab is calculated according to dose determination chart as per the SPC depending on a patient's baseline IgE level and the patient's weight.

All adult patients over the age of 16 receiving omalizumab therapy for more than one year at our local hospital, Mater Dei Hospital (MDH), the only tertiary center in Malta, were recruited for this retrospective study. These patients had been consented for any future studies related to omalizumab that may be conducted on initiation of treatment. The study was approved by University of Malta Research Ethics Committee.

Data collection was carried out between January and December 2022. This was carried out during outpatient visits, using admission and discharge notes from iSOFT Clinical Manager and Electronic Case Summary (ECS), as well as the patients' files. Data collected included demographic data, omalizumab doses received, baseline weight and IgE levels, number of exacerbations treated at home, health center or needing hospital admission, and the number of times rescue medication was needed, as well as the number of oral corticosteroids (OCS), nebulizers, and/or antibiotics required. The term exacerbation was defined as worsening of patient's symptoms from the patient's usual baseline, necessitating an increase in the usual treatment.[4]

For the purpose of this study, once data collection was concluded, our patient cohort was divided into two groups; the group that fell outside the dosing table as per the SPC due to elevated body weight and/or IgE level (who were receiving the maximum recommended dose of 600mg every 2 weeks), and the other cohort that fell within the dosing table as per the SPC (these patients were being treated and dosed according to the dosing table).

Data analysis was carried out using SPSS Statistics Version 29. Student t-test was used to compare numerical variables while a Chi-squared test was used to compare categorical variables. A p value ≤ 0.05 was taken to be statistically significant.

RESULTS

Our cohort included 71 patients (mean age at the start of treatment 48.8 ± 13.3) who had been receiving omalizumab for more than 1 year. The age range was between 16 to 74 years old, with 32 patients (45%) being male. The mean baseline IgE level was 613.2 ± 609.2 IU/ml, and the mean weight was 79.4 ± 16.7 kg. Of these, 17 patients (23.9%) had omalizumab stopped throughout the course of the treatment: 12 patients (16.9%) due to treatment inefficacy, 2 patients (2.8%) due to intolerable side-effects and 3 patients (4.2%) due to non-asthma related mortality (Table 1). Intolerable side-effects included severe myalgias and arthralgias.

Table 2 compares the demographic data and treatment discontinuation of patients receiving omalizumab treatment outside (n = 15) versus those within (n = 56) the dosing table. 4 (26.7%) patients had their treatment stopped in the outside of dosing category: 2 (13.3%) patients due to treatment inefficacy, 1 (6.7%) due to intolerable side-effects and 1 (6.7%) due to unrelated death. In the other category 13 (23.2%) patients had their treatment stopped: 10 (17.9%) patients due to treatment inefficacy, 1 (7.7%) patient due to side-effects and 2 (3.6%) patients due to mortality. There was no statistical significance between both groups with respect to treatment discontinuation (p = 0.79).

Following elimination of patients in whom treatment was stopped, 11 patients fell outside the dosing range (mean age 46.9 ± 12.3) versus 43 patients (mean age 48.1 ± 13) within the dosing table. Statistically, males predominated in the outside of dosing category (p = 0.026). The mean baseline IgE was higher in the outside of dosing category (1653.3 ± 769.8 IU/ml) compared to the other category (394 ± 261.2 IU/ml). This comparison was statistically significant (p = 0.001) (Table 3).

When comparing patients receiving omalizumab within the dosing table to those outside, the mean total number of exacerbations since initiation of treatment (1.1 ± 1.58) was significantly less for the outside of dosing category (p = 0.01). Similarly, the mean total number of OCS courses was less (0.63 ± 1.21; p = 0.02). No statistical significance was noted in the total number of hospitalizations since initiation

Table 1 *Demographic data and treatment discontinuation of total cohort of participants*

Demographic data - total cohort (n=71)	
Mean age at start of treatment (±SD), years	48.8 (13.3)
Age range, years	16 -74
Gender - males (%)	32 (45)
Mean baseline IgE (±SD), IU/ml	613.2 (609.2)
Mean weight (±SD), kg	79.4 (16.7)
Treatment discontinuation	
Treatment stopped, n (%)	17 (23.9)
Treatment inefficacy, n (%)	12 (16.9)
Intolerable side-effects, n (%)	2 (2.8)
Unrelated death, n (%)	3 (4.2)

Table 2 *Comparison of demographic data and treatment discontinuation of all patients receiving omalizumab treatment outside versus those within dosing table*

	Outside dosing range (n=15)	Within dosing range (n=56)	p-value
Demographic data			
Mean age at start of treatment (±SD) years	49.9 (12.5)	48.5 (13.6)	0.56
Age range, years	28 - 67	16 - 74	/
Gender - males (%)	12 (80)	22 (39.2)	*0.005*
Mean baseline IgE (±SD), IU/ml	1533.7 (684.7)	366.7 (245)	*<0.001*
Mean weight (±SD), kg	82 (20.4)	78.7 (15.7)	0.56
Treatment discontinuation			
Treatment stopped, n (%)	4 (26.7)	13 (23.2)	0.79
Treatment inefficacy, n (%)	2 (13.3)	10 (17.9)	0.3
Intolerable side-effects, n (%)	1 (6.7)	1 (7.7)	0.82
Unrelated death, n (%)	1 (6.7)	2 (3.6)	0.66

of treatment (p = 0.09) though this was less in the outside of dosing category (Table 4).

DISCUSSION

Allergic asthma accounts for approximately 70% of asthma, and IgE is essential in its inflammatory process. Omalizumab blocks the binding of IgE to its high affinity receptor on the surface of mast cells and basophils. Consequently, the release of inflammatory mediators is inhibited.[5,6]

Clinical studies have demonstrated that omalizumab reduces exacerbations during peak viral seasons with favourable outcomes in several randomized control trials (RCTs). In 2014, a review evaluating 25 RCTs in patients with moderate to severe allergic asthma found that omalizumab compared with placebo reduced asthma exacerbations by approximately 25%, reduced hospitalization rates, and allowed reduction of ICS doses[5,6]. In addition, a meta-analysis evaluating 86 observational studies and publications on real-world data on omalizumab, from January 2005 to October 2018, on treatment response, lung function, exacerbations, oral corticosteroid use, patient reported outcomes, health care utilisation, and school/work absence at 4, 6, and 12 months after treatment, found improvement across the board, confirming and complementing the efficacy data of such RCTs.[7]

Our retrospective study is the first of its kind to be carried out in our main local hospital and to date there is minimal literature on omalizumab treatment in asthmatic patients whose weight and/or IgE levels fall outside the dosing table. Patients who have a higher weight or IgE than that specified on the omalizumab dosing table are not usually eligible to receive such treatment in other countries.

The mean weight of our cohort who did not fall within the dosing table was still within range, suggesting that most patients would not have been eligible for omalizumab in view of the very raised IgE level, rather than the increased weight. Once removing those patients in whom treatment was stopped, results showed that males were more likely to fall outside of the dosing chart. We speculate that males are more likely to have a higher BMI, which would be in keeping with the WHO Regional Obesity Report 2022, which reports Malta as being one of the highest countries with an obese population including adults (predominantly males) and children.[8]

The original omalizumab dosing table when it was first approved had upper bodyweight and IgE limits of 150 kg and 700 IU/mL respectively. A study carried out by Kornmann et al[9] assessed the safety of omalizumab in patients with IgE/bodyweight combinations above those in the original dosing

Table 3 *Demographic data of patients in whom omalizumab was continued (removing those whose treatment was stopped)*

	Outside dosing range (n=11)	Within dosing range (n=43)	p-value
Mean age at start of treatment (±SD), years	46.9 (12.3)	48.1 (13)	0.78
Age range, years	28 - 62	16 - 68	/
Gender - males (%)	9 (81.8)	19 (44.2)	***0.026***
Mean baseline IgE (±SD), IU/ml	1653.3 (769.8)	394 (261.2)	***0.001***
Mean weight (±SD), kg	81.2 (19.3)	79.8 (16.3)	0.82

Table 4 *Comparison of asthma outcomes in patients receiving omalizumab outside versus those within the dosing table.*

	Outside dosing range (n=11)	Within dosing range (n=43)	p-value
Mean duration of treatment (±SD), years	5.45 (3.14)	6.4 (3.03)	0.4
Asthma outcomes			
Mean total number of exacerbations since start of treatment, n (±SD)	1.1 (1.58)	3.3 (4.7)	***0.01***
Mean total number of hospitalizations since start of treatment, n (±SD)	0.36 (0.67)	1.1 (2.6)	0.09
Mean total number of OCS courses since start of treatment, n (±SD)	0.63 (1.21)	2.51 (4.47)	***0.02***

table. Results overall showed 69 adverse events, none of them serious, reported by 26 patients. Analysis of laboratory measurements, vital signs and ECG data revealed no adverse findings of clinical relevance. The safety and pharmacokinetic/dynamic findings from this were consistent and supported the extension of the omalizumab dosing table to include those patients with higher IgE/ bodyweight combinations.[9] The dosing table was in fact extended to the current one being used nowadays to accommodate a higher IgE level.

The second reason for patients falling outside the dosing table is due to an elevated IgE level of more than 1500 IU/ml, as was the case in most of our patients. This implies that patients who are more likely to benefit from omali,ent improves asthma sufficiently to warrant a decrease in corticosteroid requirements, despite the patients falling outside the dosing table. These findings emphasize the clinical effectiveness of omalizumab in this cohort of patients.[12]

One may speculate that patients outside the dosing table might actually be underdosed, but our findings show that they still did comparably well in terms of exacerbation rates and number of steroid courses, as suggested by the statistically significant p values. It is known that some patients respond better than others when given omalizumab treatment. Given that only 11 patients were within the outside of dosing category, one could speculate that this could be by coincidence that this group responded better than the other cohort.

Limitations of the study included a small sample size from a single center, although representative of the whole Maltese population. There was no selection bias as all patients receiving omalizumab for more than 1 year were included in the study. However, recall bias was a limitation to this study as data was collected retrospectively. Patients could have omitted, under- or overestimated their exacerbations and symptoms, as well as steroid courses, for which they may not have been recorded in the medical notes including health center/GP visits and self-medication. Another limitation was that parameters including lung function, eosinophils, FENO, duration of asthma diagnosis, co-morbidities such as ENT pathologies, urticaria as well as asthma control questionnaires/ tests were not measured, since it is a retrospective study, therefore we could not compare both groups before treatment initiation.

Despite our cohort in the outside of dosing category is a small one, these results reaffirm the decision to treat severe IgE-mediated asthmatic adult patients with an IgE level and/or weight outside the dosing chart with the maximum recommended dose. Our study calls for the need for further larger multicenter studies to confirm that severe IgE-mediated allergic asthmatics may still receive omalizumab at the maximum recommended dose with good clinical outcomes and tolerability despite falling outside the recommended dosing table especially when alternative biologics other than omalizumab are not available, not clinically indicated or are contra-indicated. In addition, further research into the subject should include more diverse patient populations whilst investigating other biologics for severe allergic asthma.

SUMMARY BOX

- Mean total number of exacerbations was less for the outside of dosing category as was the mean total number of systemic corticosteroid courses.
- Omalizumab may be used safely outside the dosing table based on our results.
- Our results call for the need for further larger multicenter studies to confirm our findings, with the aim of potentially further expanding the dosing table.

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