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REAL-LIFE EFFECTIVENESS OF OMALIZUMAB IN SEVERE ALLERGIC ASTHMA ABOVE THE RECOMMENDED DOSING RANGE CRITERIA.

Condensed Title: Omalizumab for severe asthma above dosing range criteria.

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ABSTRACT

Background: Omalizumab (Xolair) dosing in severe allergic asthma is based on serum IgE and bodyweight. In Australia, patients eligible for omalizumab but exceeding recommended ranges for IgE (30-1500 IU/mL) and bodyweight (30-150 kg) may still receive a ceiling dose of 750 mg/4 weeks. 62% of patients receiving government-subsidised omalizumab are enrolled in the Australian Xolair Registry (AXR). **Objectives:** To determine if AXR participants above the recommended dosing ranges benefit from omalizumab, and to compare

their response to within-range participants. **Methods:** Data were stratified according to dose-range status (above or within-range). Further sub-analyses were conducted according to the reason for being above the dosing range (IgE only versus IgE and weight). **Results:** Data for 179 participants were analyzed. 55 (31%) were above recommended dosing criteria; other characteristics were similar to within-range participants. Above-range participants had higher baseline IgE [812 (IQR 632, 1747) IU/ml vs 209 (IQR 134, 306) IU/ml], and received higher doses of omalizumab [750 (IQR 650, 750) mg] compared to within-range participants [450 (IQR, 300, 600) mg]. At 6 months, improvements in Juniper 5-item Asthma Control Questionnaire (ACQ-5, 3.61 down to 2.01 for above-range, 3.47 down to 1.93 for within-range, $p < 0.0001$ for both) and Asthma Quality of Life Questionnaire (AQLQ mean score (3.22 up to 4.41 for above-range, 3.71 up to 4.88 for within-range, $p < 0.0001$) were observed in both groups. Forced expiratory volume in one second (FEV₁) improved among above-range participants. There was no difference in response between above-range and within-range participants. Above-range participants due to either IgE alone or IgE and weight had similar improvements in ACQ-5, AQLQ and FEV₁. **Conclusions & Relevance:** Patients with severe allergic asthma above recommended dosing criteria for omalizumab have significantly improved symptom control, quality of life, and lung function to a similar degree to within-range participants, achieved without dose escalation above 750 mg. (Abstract word count 300 words.)

Introduction

Severe asthma affects 5-10% of asthma patients but confers disproportionate morbidity and mortality [1]. More efficacious treatments are needed for these patients in whom standard therapies based on high dose corticosteroids and long-acting β_2 -agonists do not achieve satisfactory asthma control [2]. It is now apparent that severe asthma is heterogeneous, and a

number of different phenotypes have been identified [3,4,5]. Accurate phenotyping in severe asthma is important to allow selection of the most appropriate therapy [6,7,8].

The anti-IgE monoclonal antibody omalizumab (Xolair) provides safe and effective targeted therapy for the severe allergic asthma phenotype [9,10,11,12]. Its mechanism of action is believed to involve its ability to bind with free circulating IgE to form inert IgE-anti-IgE complexes, reducing IgE binding to high affinity IgE receptors (FcεRI) on mast cells and other effector cells [13]. Total serum IgE has been the biomarker of choice to identify the allergic phenotype, and to predict treatment-responsiveness [14].

Total serum IgE is also used to calculate the necessary dose of omalizumab for an individual patient. Omalizumab dosing is designed to achieve free IgE levels of no more than 20.8 IU/ml, and preferably less than 10.4 IU/ml [15]. The required subcutaneous drug dose in milligrams per 4-week cycle is based on an individual's pre-treatment total serum IgE and body weight [0.016mg/kg/IU (IgE/ml)]. Standard dosing tables recommended a ceiling of 750 mg per 4-week cycle and in previous pivotal studies, patients in whom IgE and weight resulted in a calculated dose of > 750mg per 4-week cycle did not receive omalizumab [15, 10]. This approach continues to apply in the United States [13, 16].

In Europe, an extended dosing schedule allowing up to 1200 mg per 4-week cycle has been introduced, based on pharmacodynamic and bronchial hyper-reactivity studies [17,18, 19]. Yet even with the extended dosing range, 24 % of otherwise suitable patients remain ineligible for treatment due to an excessive body weight-serum IgE product [20].

In Australia, the approved Product Information for omalizumab states that it is indicated for patients with IgE levels corresponding to the recommended dose range, but it also provides advice about how to use a formula to select doses for patients whose bodyweight and IgE lie above the dosing table; these are the patients of interest in the present analysis. Omalizumab

is government-funded in Australia for patients over 12 years of age with severe allergic asthma who meet specific initiation criteria (Online Supplement S1), with the recommended maximum dose being 750mg per 4-week cycle [21]. Patients whose calculated dose exceeds the specified dosing criteria may still be prescribed 750 mg. In theory, these patients are under-dosed for their body-weight and serum IgE level.

Of direct relevance, evidence is now emerging for the effectiveness of omalizumab in allergic conditions with IgE levels elevated beyond standard dosing recommendations. Omalizumab demonstrated significant clinical and immunological benefit in patients with Allergic Broncho-Pulmonary Aspergillosis (ABPA) and IgE levels up to 5000 IU/ml [22].

This led us to hypothesise that patients with severe allergic asthma whose IgE and/or body weight lie above the recommended dosing criteria would still experience clinical benefit from the ceiling dose of 750 mg per 4-week cycle.

In Australia, the majority of patients receiving government-funded omalizumab are enrolled in the Australian Xolair Registry (AXR), a post-marketing registry which serves as a ready source of centralised data [23]. We therefore tested our hypothesis among AXR participants whose body weight and/or serum IgE were above the ranges in the recommended dosing table. We also compared the treatment response in above-range participants with within-range participants to determine if the responses were significantly different.

Methods

The AXR is an investigator-initiated and investigator-led multi-centre observational study that recruits patients with severe allergic asthma who are being assessed for eligibility and commencement of omalizumab through the Pharmaceutical Benefits Scheme (PBS). (The

PBS an Australian government programme which subsidises prescription medication.)

Patients who receive approval for government-subsidised therapy are assessed for treatment-responsiveness at six months to determine eligibility for continuation (Online Supplement, S1). All participants included in this analysis received omalizumab following approval from the PBS and Medicare. (Medicare is an Australian government programme which provides access to medical services for Australian residents.)

Following AXR enrolment, participant treatment and follow-up is continued at the discretion of the treating physician in accordance with Australian standard medical practice and local reimbursement requirements, and is independent from the study. All participants provided written informed consent prior to entry in the AXR.

The AXR involves 21 sites throughout Australia. Ethics approval was granted by the lead site; the Hunter New England Human Research Ethics Committee (reference 11/10/19/5.03).

All patients who meet the eligibility criteria for government subsidised omalizumab are eligible for enrolment in the AXR. The enrolment period is approximately 2 years, with each patient having a follow-up observation period of up to 2 years after the start of omalizumab treatment. Upon enrolment in the registry, data including demographics, medical history, disease status and control, current treatment, lung function, medical resource use over the last year prior to the start of omalizumab treatment, and patient reported outcomes [(the Juniper 5-item Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire (AQLQ)] are entered from the patients' medical assessment or AXR data collection [23,24].

An ACQ-5 score under 0.75 indicates well-controlled asthma, and above 1.5, inadequately controlled asthma, over the previous week [25]. A change in ACQ-5 of 0.5 is considered the minimal clinically important difference [25], and is one of the criteria used for continuation of government-sponsored treatment. The AQLQ score is the mean of 32 disease specific

quality of life questions, questions relate to the last 2 weeks and assess 4 domains including symptoms, activity limitation, emotional function and environmental stimuli, with a lower AQLQ representing greater impairment of health status. A change in AQLQ total score of 0.5 from baseline represents a clinically meaningful change [26].

Patients are reassessed and data entered in the AXR database at approximately 6 months, 12 months, 18 months and 24 months after the start of omalizumab treatment. Initial cross-sectional data and 6 month follow-up will be reported elsewhere.

For the present analysis, AXR participants were classified according to their baseline weight and/or IgE level, that is whether these variables lay below or above the upper limit specified in the dosing table for government-subsidised treatment (Figure 1).

The primary outcome for analysis at six months was the change in symptom control measured by ACQ-5 following 6 months of omalizumab treatment. Since this is one of the criteria for eligibility for continuation of government approved and funded omalizumab beyond 6 months, it was therefore recorded and available in almost all AXR participants.

Secondary outcomes were the changes in AQLQ mean score and pre and post-bronchodilator forced expiratory volume in one second (FEV₁) percent predicted. Because these data were not required for continuation of government-funded omalizumab, they were only available at baseline and 6 months in a proportion of participants.

The AXR also recorded changes in hospital admissions and exacerbations in a small proportion of participants. These were not specified as study outcomes; the reliability of the data was uncertain as they were based on retrospective patient recall.

The treatment response to omalizumab for above-range patients was compared with that of within-range patients by analysing range status (either above-range or within-range) as a

predictor for ACQ-5, AQLQ, and FEV₁% predicted, when adjusted for age, gender, site, and dose of omalizumab.

A sub-analysis was conducted according to the reason for being above the dosing range (IgE only versus IgE and weight combined).

Statistical analysis

All analyses were conducted using STATA 13 (College Station, Texas, USA). Participants were classified by whether their baseline weight and IgE were within or above the omalizumab dosing range. Changes in ACQ-5, AQLQ score, and pre and post-bronchodilator FEV₁ percent predicted between baseline and 6 months were calculated for these participants.

Baseline comparisons were conducted using Chi² or Fisher's exact test for categorical data, and Student's t-test or Wilcoxon rank sum test for continuous data as appropriate. Paired analyses were conducted on baseline and follow-up clinical, quality of life, and medication data to determine response to omalizumab treatment. McNemar's Chi² or exact test for categorical or Wilcoxon sign rank test for continuous data were conducted for the paired analyses. Further analysis for the difference between baseline and follow-up visit was conducted using Student's t test or Wilcoxon rank sum test. A p-value <0.05 was considered significant.

Multiple linear regression was performed for change in ACQ, AQLQ & FEV₁% predicted with dosing range status and omalizumab dose as covariates, and adjusted for age, gender and site.

Results.

Baseline data.

Enrolled in the registry were 179 participants who received approval to commence omalizumab and had 6 month data for comparison. This comprised 62% of patients receiving government-funded omalizumab nationally [20]. Of the participants who commenced treatment, 55 (30.7%) were above the recommended Australian dosing range; 21 due to IgE alone, 33 due to IgE and weight, and one for weight alone.

Registry participants within and above the dosing range were similar with respect to demographics, asthma medication, lung function and baseline asthma control measured by the ACQ-5 (Table 1). Of note, baseline ACQ-5 and BMI were not significantly different (Table 1). However, baseline total serum IgE was significantly higher at 812 (IQR 632, 1747) IU/ml in above-range participants versus 209 (IQR 134, 306) IU/ml in within-range participants, and asthma quality of life measured by the AQLQ score was significantly poorer [3.21, (SD 1.14) in above-range participants versus 4.01 (SD 1.21) in within range participants (, $p=0.02$)].

Participants above the recommended dosing range received a higher median (IQR) omalizumab dose of 750 (650, 750) mg, compared to those within the range who received 450 (300, 600) mg . The maximum dose received was 750 mg.

All 55 participants above the Australian dosing range would be considered above-range in the United States and would not receive treatment. Of these, 36 were also above the extended dosing range in current use in the European Union (Figure 1).

Change from baseline to six months.

Following six months of treatment, there was a significant improvement in asthma control in participants with IgE and/or weight above the dosing range (ACQ-5 3.61 down to 2.10, $p < 0.0001$) comparable to participants within the range (ACQ-5 3.47 down to 1.93, $p < 0.0001$, Figure 2). There was no difference in the proportion of participants experiencing a clinically important reduction in ACQ-5 of ≥ 0.5 , 84.0% of above-range participants and 78.0% of within-range participants ($p=0.38$).

In above-range participants, the AQLQ significantly improved (3.22 up to 4.41, $p < 0.001$, Figure 2). There was no difference between the proportion of above-range (72.7%) and within-range participants (64.4%) who achieved a clinically important increase in AQLQ ≥ 0.5 ($p= 0.49$).

In above-range participants, there were improvements in pre-bronchodilator FEV_1 % predicted (54.8% to 64.0%, $p<0.05$) and post-bronchodilator FEV_1 (63.9% to 73.1%, $p=0.05$) with no difference in improvement between within-range and above-range participants ($p=0.147$ and $p=0.214$ for pre and post-bronchodilator comparisons respectively).

There was no reduction in hospital admissions in above-range participants ([from 0.5 (0, 0.5) to 0 (0, 1), $n=20$, $p=0.182$] but a slight increase in admissions among within-range participants [from 0 (0, 0.5) to 0 (0, 1), $n=42$, $p=0.01$]. There was no change in exacerbation rate in above-range [from 0.55 (0.22) to 0.85 (1.45) exacerbations/person/6 months, $n=52$, $p=0.143$] or within-range participants [0.49 (0.27) to 0.52 (0.84) exacerbations/person/6 months, $n=118$, $p=0.719$].

Above-range participants compared to within-range participants.

The treatment response to omalizumab for above-range patients when compared to within-range participants was not statistically different in terms of ACQ-5, AQLQ and FEV₁% predicted (pre and post-bronchodilator), adjusted for age, gender and site (Table 2).

Omalizumab dose was included as a covariate in this analysis, and higher doses were associated with a statistically significant greater reduction in ACQ-5 (correlation coefficient - 0.002, SE 0.001, p=0.03, Table 2).

Sub-analysis of above-range participants.

The sub-analysis comparing participants above range due to IgE alone (38.2%) versus IgE and weight (60%) demonstrated similar improvements in ACQ-5, AQLQ and FEV₁, although many values were no longer significant due to the small numbers in each group (Table 3).

There was no difference in the proportion of participants experiencing a clinically significant reduction in ACQ-5 of ≥ 0.5 , 19/20 (95.0%) of participants above-range due to IgE alone participants and 22/29 (75.9%) of participants above-range due to IgE and body-weight (p=0.12). Only one participant (1.8%) was dosed above range due to high weight alone in the absence of elevated IgE.

Adverse events.

Three above-range participants discontinued omalizumab due to adverse events, one of which was anaphylaxis. Two within-range participants discontinued omalizumab due to adverse events, one of which was anaphylaxis.

Discussion

In AXR participants with severe allergic asthma whose body weight and baseline serum IgE place them above the recommended dosing range for omalizumab, our data demonstrates real-life benefit without their having had dose escalation beyond 750 mg per 4-week cycle, the recommended ceiling dose funded in Australia (Figure 2). The magnitude of clinical improvement in these participants was not significantly different to that in those within the dosing range (Table 2). In a sub-analysis, participants above the dose range due to a high IgE alone had similar benefits to those above range due to both high IgE and body weight (Table 3).

The mean omalizumab dose was higher in above-range participant group (Figure 1). When omalizumab dose was assessed as a predictor of response, there was a statistically significant association ($p=0.03$) between higher doses and a greater reduction in ACQ-5 at six months, regardless of dose range status (Table 2). This is an interesting finding which warrants examination in other similar cohorts.

The proportion of registry participants above the dosing range was substantial (55 individuals, or 31% of the cohort). In the United States, such patients are not currently eligible for omalizumab treatment [17]. Of these, 36 (comprising 20% of the entire cohort) were also above the extended dosing schedule now in use in the European Union which permits up to 1200 mg/4-week cycle. Similar proportions of patients with allergic asthma above the dosing range have been reported elsewhere [20].

The extended dosing schedule in Europe is based on surrogate outcomes comprising pharmaco-dynamic modelling and studies of bronchial hyper-reactivity [18, 19]. In contrast, our analysis focuses on clinically relevant endpoints important to asthma patients, and demonstrates benefit at, or close to, ceiling doses.

Our findings add another dimension to the continuing debate around the pharmacologic mechanisms of anti-IgE treatment in asthma. The extended dosage schedule is based on data modelling which aims to achieve suppression of free IgE to below 20.8 IU/ml, which is considered necessary for clinical effect [15,27]. In our registry, we do not have data on serum free IgE levels following omalizumab treatment. If free circulating IgE *was* suppressed in our cohort by doses of 750 mg, published pharmaco-dynamic modelling may be over-estimating the necessary drug dosage required to achieve this target.

If free circulating IgE *was not* suppressed below 20.8 IU/ml, then perhaps this magnitude of IgE suppression is not essential to produce a clinical therapeutic benefit, whether that benefit is delivered by blocking IgE effects on mast cells, basophils, or plasmacytoid dendritic cells [28].

An alternative explanation is that some of the observed benefit of omalizumab in this study was independent of IgE-mediated pathways. This would be consistent with studies showing efficacy for omalizumab in non-atopic asthma and chronic urticaria, conditions where IgE is not considered central to disease pathogenesis [29,30]. In such a case, future strategies to predict response to omalizumab may be more reliant on biomarkers other than IgE, such as the fraction of exhaled nitric oxide, peripheral blood eosinophil count, and serum periostin, for which there are preliminary data [31].

The practical implications of our findings differ according to the prescribing context. Firstly, in Australia, our results justify the current dosage regimen, at least until greater patient data accrual allows further stratification of outcomes. Current product information from the Therapeutic Goods Administration states that “doses greater than 750 mg were not studied in the pivotal clinical studies and are not recommended” [32]. Therefore, when criteria for government-subsidised treatment with omalizumab were developed, patients above the

dosing range received the ceiling dose of 750 mg. Our data supports the real-life effectiveness of the 750 mg dose in patients above the dosing range, without further dose increase.

Secondly, for countries such as the United States where patients above the dosing range are currently ineligible to receive omalizumab, our data, if confirmed by prospective controlled studies, suggests such exclusion may bear reconsideration.

Thirdly, in jurisdictions such as the European Union where an extended dosing schedule has already been adopted, our data suggest that such dose increases may not be necessary to achieve satisfactory clinical response. Given the high cost of omalizumab treatment, determining the minimally effective dose of omalizumab to achieve acceptable clinical asthma outcomes may offer long term health care savings [33,34].

This study bears the usual constraints of registry data, and more concrete research is required to address the question of omalizumab effectiveness in the above-range severe asthma population. Enrolment into the registry was not mandatory, however, the AXR captured 62% of patients receiving government-subsidised omalizumab nationally [33]. Improvements in asthma control based on patient questionnaires are subject to bias, especially when administered following open-label treatment without a control group. However, the magnitude of asthma control improvement in the above-range participants was similar to that of participants within the dosing range. Additionally, significant improvements in lung function and quality of life were also seen, supporting a real clinical benefit. Admission rates and exacerbations were not improved at six months for either within-range or above-range participants, but these data were available for only a minority of participants, and obtained by retrospective (and uncertain) patient recall.

In conclusion, patients with severe allergic asthma whose IgE and/or weight are above the recommended dosing table criteria appear to benefit from omalizumab, without dose escalation beyond 750 mg per 4-week cycle. Above-range participants derived a clinical benefit which was not significantly different to that of within-range participants. Previous studies supporting extended dosing up to 1200 mg were based on pharmaco-dynamics and bronchial hyper-reactivity, but our study demonstrated improvements in important clinical outcomes relevant to patients with doses capped at 750mg. Prospective controlled studies are warranted to confirm the preliminary findings from our cohort.

Acknowledgements and Conflicts of Interests

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Table 1. Baseline characteristics of subjects within or above omalizumab dosing range.

	N	Within dose table range	N	Above dose table range	p-value
Age ^α (all > 12)	124	52.0 (14.6)	55	50.3 (16.0)	0.49
Male:Female		49:75		17:38	0.27
ACQ-5 score ^α	115	3.56 (1.06)	54	3.63 (0.72)	0.66
Smoking: [¥]	92		47		0.72
Never		67 (72.8%)		32 (68.1%)	
Current		2 (2.2%)		2 (4.3%)	
Ex		23 (25.0%)		13 (27.7%)	
Pack years ^β	17	23.0 (6.0, 47.5)	9	1.5 (1.0, 20.0)	0.10
Weight, kg; ^β	124	79.6 (69.0, 91.7)	55	86.0 (65.5, 107.9)	0.15
BMI, kg/m ² ^β	121	29.0 (25.7, 33.5)	53	32.1 (24.7, 39.8)	0.19
*Atopy [¥]	124	123 (99.2%)	55	53 (96.4%)	0.17
Admission past 12 months, n(%)	117	35 (29.9%)	52	24 (46.2%)	0.041
No. of exacerbations, median (Q1,3)	124	1 (1,1), 0-3	55	1 (1, 1), 0-3	0.160
**Maintenance OCS (oral corticosteroid) use [¥]	121	56 (46.3%)	53	33 (62.3%)	0.052
OCS dose (mg/day), ^β range	56	10.0 (7.5, 17.5)	32	10.0 (10.0, 16.0)	0.59
ICS (Inhaled Corticosteroid) [¥]	122	118 (96.7%)	54	4 (90%)	0.072
ICS dose (BDPmcg/day) ^β	116	2000 (1600, 2280)	45	2000 (1600, 2000)	0.51
Long Acting ^β Agonist [¥]	123	116 (94.3%)	55	45 (88.2%)	0.17
Short Acting Anticholinergic [¥]	123	15 (12.2%)	55	3 (5.5%)	0.28
Long Acting Anticholinergic [¥]	124	24 (19.4%)	54	10 (18.5%)	0.89
Leukotriene Modifier [¥]	123	14 (11.4%)	54	4 (7.4%)	0.59
Nasal Corticosteroids [¥]	124	15 (12.1%)	55	4 (7.3%)	0.43
Short Acting ^β Agonist [¥]	119	68 (57.1%)	49	27 (55.1%)	0.80
Theophylline [¥]	123	6 (4.9%)	55	1 (1.8%)	0.43

* defined as positive skin prick testing or detection of specific IgE on blood testing.. ^α mean (SD), student's t-test; ^β median (Q1,Q2), Wilcoxon ranksum test; [¥] n(%),chi² or Fisher's exact test.
ACQ-5; five-item asthma control questionnaire, BMI; body mass index

Table 2. Multiple linear regressions for change in ACQ, AQLQ & FEV1% with dose range status and omalizumab dose as covariates, and adjusted for age, gender, and site.

	N	Above dosing range Coefficient (SE)	p- value	Omalizumab dose Coefficient (SE)	p- value
Δ ACQ5 score	159	0.39 (0.30)	0.189	-0.002 (0.001)	0.030
Δ AQLQ mean score	67	-0.69 (0.52)	0.189	0.001 (0.001)	0.296
Δ FEV1 % predicted (Pre BD)	67	1.18 (7.65)	0.878	0.03 (0.02)	0.221
Δ FEV1 % predicted (Post BD)	41	1.45 (10.04)	0.886	0.02 (0.03)	0.576

FEV1; forced expiratory volume in one second, ACQ-5; 5 item asthma control questionnaire, AQLQ; asthma quality of life questionnaire, BD; bronchodilator

Table 3. Sub-analysis: Baseline to 6 months comparison for participants above the omalizumab dosing range for IgE only versus IgE & weight

	Above IgE range only				Above IgE & weight range			
	N	Baseline	6 months	P value	N	Baseline	6 month	P value
Omalizumab dose	19	750 (750, 750)	750 (750, 750)		23	750 (600, 750)	750 600, 750)	0.317
ACQ-5 score ^α	20	3.55 (0.76)	1.82 (1.20)	<0.0001	30	3.65 (0.78)	2.13 (1.07)	<0.0001
AQLQ mean score ^α	6	3.27 (0.96)	4.76 (1.37)	1.00	16	3.21 (1.33)	4.30 (1.14)	0.001
FEV ₁ % predicted (Pre BD) ^α ;	9	43.26 (13.91)	62.59 (23.48)	0.048	15	61.84 (21.39)	64.81 (23.56)	0.306
FVC % predicted (Pre BD) ^α ;	9	74.13 (4.55)	87.58 (22.77)	0.118	15	80.76 (22.61)	83.29 (21.84)	0.466
FEV ₁ /FVC (Pre BD) ^α	9	46.89 (15.21)	58.59 (17.12)	0.100	17	61.39 (11.40)	61.56 (12.0)	0.925
OCS use [¥]	21	11 (52.38%)	9 (42.86%)	0.500	30	20 (66.67%)	20 (66.67%)	1.0
OCS dose (mg/day), ^β	9	10 (10, 12.5)	10 (7, 12.5)	0.473	17	10 (10, 17)	10 (10, 25)	0.823

IgE:Immunoglobulin E, FEV₁; forced expiratory volume in one second, FVC; forced vital capacity, ACQ-5; 5 item asthma control questionnaire, AQLQ; asthma quality of life questionnaire, OCS; oral corticosteroids, BD; bronchodilator. ^α mean (SD), student's t-test; ^β median (Q1,Q2), Wilcoxon ranksum test; [¥] n(%),chi² or Fisher's exact test.

		Weight (kg)								
		30-40	40-50	50-60	60-70	70-80	80-90	90-125	125-150	>150
Total IgE (IU/ml)	30-100	150	150	150	150	150	150	300	300	1
	100-200	150	300	300	300	300	300	450	450	
	200-300	300	300	300	450	450	450	600	600	
	300-400	300	450	450	450	600	600	2	1	
	400-500	450	450	600	600	750	750	3		
	500-600	450	600	600	750	1	1	2		
	600-700	450	600	750			3	6	2	
	700-800	600	750		1	2		2		
	800-900	600	750	1	1			1		
	900-1000	750		1		1	1	1		
	1000-1100	750								
	1100-1200				1					
	1200-1300				1	1				
	1300-1500					1				
	>1500	1		5	4	1	2	3	1	

Figure 1- Weight and total IgE of participants above the recommended dosing tables for omalizumab.

Purple- Standard dosing range (eg Australia and United States) with recommended doses in mg per 4-week cycle; Yellow- Extended dosing range (eg European Union), with numbers of patients in each box; Light blue- outside extended dosing range, with numbers of patients in each box. In the United States, the omalizumab Product Information states “Do not dose” for patients outside the purple zone. In Australia, patients outside the purple zone, if otherwise eligible, may be prescribed a maximum of 750mg per 4 week cycle.

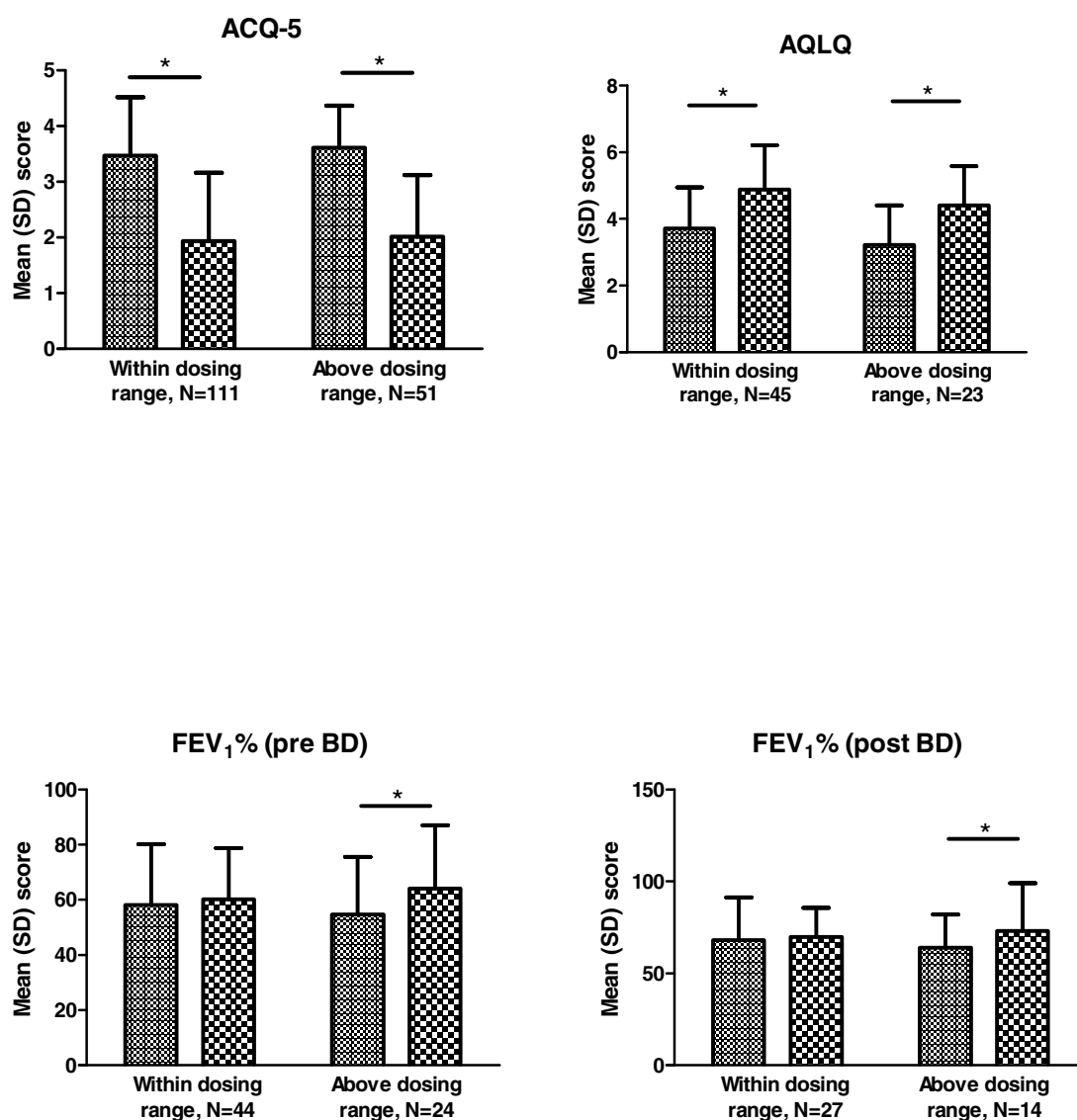


Figure 2. Change in ACQ-5, AQLQ, FEV₁ % predicted (pre-bronchodilator) and FEV₁ % predicted (post-bronchodilator) after 6 months of omalizumab treatment among patients within and above the recommended dosing range. . █ Baseline; █ 6 months, *p<0.05

IgE:Immunoglobulin E, FEV₁; forced expiratory volume in one second, ACQ-5; 5 item asthma control questionnaire, AQLQ; asthma quality of life questionnaire, BD; bronchodilator.