

The real-life clinical effects of 52 weeks of omalizumab therapy for severe persistent allergic asthma

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Abstract *Background* Omalizumab was introduced in Malta in 2011. To date, no local data have been published. *Objective* To obtain baseline characteristics of our local cohort, determine effectiveness of omalizumab at 52 weeks, compare clinical outcomes 52 weeks pre- and postomalizumab therapy and to assess its safety and tolerability. *Setting* The Mater Dei Hospital in Malta. *Method* All consented adult patients who were eligible to start treatment with omalizumab for asthma were enrolled in this open, prospective observational real-life study. A questionnaire was completed and an Asthma Control Test and spirometry performed. Patients were reviewed on a regular basis. Any undesirable symptoms were recorded. Treatment effectiveness was evaluated at 16 and 52 weeks, during which a decision was taken whether patients were responders. Outcomes were compared 52 weeks pre- and post-treatment initiation. *Main outcome measure* To determine effectiveness of treatment following 1 year of omalizumab by assessing its impact on the rate of asthma-related exacerbations and health care utilization including hospitalizations. *Results* Our cohort included 22 patients, all non-smokers (mean age 52.7 ± 11 , 64 % males). The mean baseline IgE level was

448.6 ± 444 IU/ml. At week 12, treatment was stopped in one patient due to arthralgias. The drug was stopped in two patients at week 16 due to treatment ineffectiveness. At week 20, treatment was stopped in another patient in view of arthralgias. A significant reduction in the number of asthma exacerbations ($p = .03$) and number of systemic steroid courses required ($p = .03$) was identified at 52 weeks. There was a significant improvement in the ACT score ($p < .001$) after 52 weeks but no significant improvement in FEV1. There was a non-significant decline in the number of hospitalizations ($p = .6$), asthma-related healthcare visits ($p = .2$) and days off work ($p = .09$). Adverse events occurred in 10 % of patients. Costs related to asthma hospital-stay and medicines administered during hospitalisations were decreased by half following 1 year on omalizumab. *Conclusion* Omalizumab treatment resulted in an improved asthma control, with a significant reduction in asthma exacerbations and systemic steroid courses required and improvement on ACT score. Adverse events were infrequent and the drug was well tolerated.

Keywords Anti-IgE antibodies · Health care utilizations · Omalizumab · Allergic asthma · Tolerability · Effectiveness

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Impact of findings on practice

- For prescribing omalizumab, rigid criteria must be formulated.
- Reduction in the use of OCS can have an indirect benefit in terms of reduction of longterm effects of steroids, which still need to be quantified in relation to omalizumab.

Introduction

Omalizumab is a humanised anti-immunoglobulin E (IgE) monoclonal antibody licensed in the European Union for patients aged ≥ 6 years with severe allergic asthma inadequately controlled with inhaled corticosteroids and long-acting B_2 agonists [1] as per GINA step 4 therapies [2]. Severe asthma is defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming “uncontrolled” or that remains “uncontrolled” despite this therapy [3]. The efficacy and safety of omalizumab in uncontrolled severe allergic asthma has been demonstrated in a number of randomised studies [4–9], as well as ‘real-world’ studies [9–16]. Due to its mechanism of action, the European Medicines Agency (EMA) recommends that omalizumab treatment effectiveness be assessed after 16 weeks of treatment [17]. Omalizumab was originally assessed by the Maltese health technology appraisal body in 2010 and introduced on the formulary list in 2011. To date, no local data has been published. Rottem (2012) suggested that ‘real-life’ studies are important to determine who will most benefit from omalizumab treatment [18].

Aim of the study

The primary objectives of this study were to: (1) obtain baseline characteristics of our local cohort, (2) determine effectiveness of omalizumab at 52 weeks, (3) compare clinical outcomes 52 weeks pre- and post- omalizumab therapy and (4) assess the safety and tolerability of omalizumab therapy. The following secondary objectives were assessed: (1) the economic impact related to healthcare resource utilization and days off work, (2) the efficacy and tolerability of omalizumab in patients requiring out-of-range doses from those recommended by the Summary of Product Characteristics (SmPC) [19].

Ethical approval

Human subjects’ approval for the study was obtained from the University Research Ethics Committee, University of Malta. Permission was obtained from the caring respiratory consultants and the Chairman of the department of medicine.

Methods

Study design

This prospective observational study was designed to analyse the 52 week clinical effectiveness, safety, tolerability and cost

effectiveness of omalizumab as add-on treatment in patients with severe persistent allergic IgE-mediated asthma in a ‘real-life’ clinical setting in Malta.

Inclusion criteria

All adult patients who were eligible to start treatment with omalizumab for asthma at the Mater Dei Hospital, the only referral centre for such treatment in Malta, were consented and enrolled in this prospective observational study. Adult patients with uncontrolled severe IgE-mediated allergic asthma despite compliance with high doses of inhaled steroids and long acting B_2 -agonist with a satisfactory inhaler technique and a high IgE level, reduced FEV₁, frequent day- or night-time symptoms and recurrent exacerbations during the previous year were identified by respiratory consultants as ideal candidates. Study eligible patients included all patients who were expected to complete 52 weeks of omalizumab between 2011 and 2013.

Data collection

A baseline visit with the principal investigator was organised, during which patients were consented to start treatment, a questionnaire completed and an Asthma Control Test (ACTTM) [21] and spirometry performed. The first part of the questionnaire included (a) demographic data (b) smoking history and (c) co-morbidities. The second part was related to data on the 12-month period prior to starting omalizumab treatment (number of asthma exacerbations and asthma-related hospitalisations, number of oral corticosteroids (OCS), number of unscheduled asthma-related doctor visits and days off-work). The last part of the questionnaire included (a) drug history, (b) lung function tests and (c) blood investigations (full blood count, erythrocyte sedimentation rate, C-reactive protein, renal and liver profile).

Patients were reviewed every 4 weeks until week 16 and every 8 weeks thereafter. Each review coincided with the date scheduled for receiving the drug. During each clinical review, a further questionnaire including an ACT, was completed and included change in asthma-related medication, asthma-related events including exacerbations, unscheduled health care visits, hospitalizations and OCS courses required. Any undesirable symptoms were also recorded.

A clinically significant asthma exacerbation was defined as worsening of asthma as judged clinically significant by the physician, requiring an increase in asthma-related medication for more than 1 day.

Medication and dosage

Omalizumab dosages were determined based on the patients’ weight and IgE level. For patients who had an IgE

level exceeding the recommended dosing table, the dose administered was that according to the highest recommended dose based on that weight [19].

Outcome measures

Clinical outcomes included comparison of number of exacerbations, hospitalizations, unscheduled health care visits, number of OCS courses prescribed, and dose reductions in OCS between 52 weeks pre- and post-omalizumab therapy. The ACT score, FEV₁ and blood samples were also compared.

Measurement of treatment effectiveness

After 16 weeks of treatment with omalizumab, the treating physician determined whether omalizumab was to be continued, depending on the global evaluation of treatment effectiveness (GETE) scale [21]. The GETE is graded as follows: excellent (complete control of asthma, good (marked improvement of asthma), moderate (discernible, but limited improvement in asthma), poor (no appreciable change in asthma), worsening (overall deterioration in asthma control). Responders were classified if they had an excellent or good response. These patients were monitored and response was re-evaluated after 52 weeks.

Measurement of asthma control

Asthma control was assessed using an English version of the five point ACT and provides subjective perspective of asthma control. An overall ACT score ≤ 19 was found to identify patients with inadequately controlled asthma and a score ≤ 15 predicted uncontrolled asthma [22].

Measurement of lung function

Lung function was evaluated by measurement of initial forced expiratory volume in 1 s (FEV₁) at the pulmonary function lab.

Measurement of costs related to resource utilisation and days off work

Healthcare resource utilization was captured for 1 year prior to enrolment and for the following 52 weeks whilst on omalizumab. This included the cost for: (a) asthma-related hospitalisations, which included the cost for hospital stay (256.23 euro per night as indicated by Mater Dei Hospital's billing section) [23] and medicines required during the stay as per British National Formulary 2014 prices [24], (b) cost of OCS courses; (c) cost for unscheduled doctor visits (10 euro per visit) [25]. Costs related to days off work was calculated based

Table 1 Baseline characteristics

Baseline characteristics	n = 22
Age (years)	
Mean (SD)	52.7 (11)
Median (range)	55 (26–74)
Gender n (%)	
Male	14 (64)
Female	8 (36)
Race n (%)	
Caucasian	21 (95)
Other	1 (5)
Employment status n (%)	
Unemployed	8 (36.4)
Employed	7 (31.8)
Housewives	6 (27.3)
Retired	1 (4.5)
Weight (kg)	
Mean (SD)	82 (16.4)
Median (range)	81.5 (51–120)
Smoking history n (%)	
Current smoker	0 (0)
Former smoker	10 (45)
Never smoked	12 (55)
FEV ₁ (% predicted)	
Mean (SD)	66.3 (22.9)
Median (range)	64 (28–27)
Total IgE (IU/mL)	
Mean (SD)	448.6 (444)
Median (range)	318 (52.7–1,800)
ACT total	
Mean (SD)	13.9 (6)
Median (range) x (y–z)	12 (5–25)
Days off work in the previous year	
Mean (SD)	4 (2.2)
Median (range)	0 (36)
Exacerbations in the previous year	
Mean (SD)	4.6 (3.8)
Median (range)	3 (0–12)
Hospitalizations in the previous year	
Mean (SD)	0.72 (1.6)
Median (range)	0 (0–7)

on the Maltese monthly gross average wage of 1,311 euro (National Statistics Office Labour Force survey: Q2/2013) [26].

Statistical methods

Data generated from the questionnaire were analysed by determining frequency distributions, graphic displays and

descriptive statistics which will include mean $\pm$ standard deviation (SD). Data was analysed using Microsoft Excel 2010®. A p value of $<.05$ was taken to be statistically significant. Two-tailed paired sample student t -tests were used to obtain p values. Confidence intervals were calculated using the Newcombe–Wilson method without continuity correction. Patients who discontinued omalizumab were not included in the 52 week analysis.

Results

Baseline characteristics

A total of 22 patients with uncontrolled severe persistent allergic asthma were identified as ideal candidates for omalizumab treatment. Their baseline characteristics are shown in Table 1. All had a satisfactory inhaler technique and were compliant to their medication. Common comorbidities amongst our patients included osteoporosis and allergic rhinitis ($n = 5$, 23 %), systemic hypertension ($n = 4$, 18 %), eczema ($n = 3$, 14 %), diabetes mellitus ($n = 2$, 9 %), ischaemic heart disease/congestive heart failure ($n = 1$, 4.5 %). Others included hyperlipidaemia, anxiety and depression. They were all at Stage 5 of the GINA guidelines [2].

Asthma-related medication at presentation included high dose inhaled corticosteroids (≥ 1000 mcg/day) and a long-acting β_2 -agonist in all patients. Five patients (23 %) were receiving a leukotriene receptor antagonist and four patients (18 %) had failed a therapeutic trial. Nine patients (41 %) were on maintenance prednisolone, dose ranging between 5 and 20 mg. Three patients (14 %) were on theophylline and seven patients (32 %) were on ipratropium bromide.

Effect of omalizumab on asthma control and treatment effectiveness

A comparison of the ACT at baseline and 16, 32 and 52 weeks of treatment are demonstrated in Fig. 1 and the GETE in Fig. 2. ACT score varied from a mean of 14 at 0 weeks, 21 at 16 weeks ($p < .001$, 95 % CI -9.73 to -3.67), 20.6 at 32 weeks ($p < .001$, 95 % CI -9.65 to -2.75) and 20 at 52 weeks ($p < .001$, 95 % CI -8.94 to -1.86).

Effect of omalizumab on clinical outcomes

Table 2 demonstrates the effect of omalizumab on number of exacerbations, hospitalizations, number of asthma-related unscheduled health care visits and number of systemic OCS prescribed.

Effect of omalizumab on lung function

The mean FEV₁ at baseline was 68.2, 72.6 % at 16 weeks ($p = .34$, 95 % CI -19.03 to 10.23) and 68.4 % ($p = .97$, 95 % CI -14.88 to 13.88) at 52 weeks in the responder group. Following 52 weeks of treatment only 50 % of patients showed an actual improvement in their FEV₁. FEV₁ was not compared at 32 weeks since three patients failed to do spirometry at this stage.

Effect of omalizumab on medication reduction

Of the 41 % ($n = 9$) of patients on OCS, omalizumab was stopped in 9 % ($n = 2$), 9 % ($n = 2$) reduced their daily OCS, 9 % ($n = 2$) did not manage to reduce the dose in the long term and 13.6 % ($n = 3$) stopped the systemic corticosteroids altogether. No attempts were made at reduction of inhaled corticosteroid doses, long acting B_2 -agonist, theophylline and leukotriene receptor antagonists dosages.

Effect of omalizumab on blood indices

Among the responders, there was a non-statistically significant decline in the mean eosinophil count, $.74\text{--}0.38 \times 10^9/\text{L}$ ($p = .08$, 95 % CI $-.15$ to $.73$) at week 16 and to $.42 \times 10^9/\text{L}$ ($p = .1$, 95 % CI $-.91$ to $.69$) at week 52. Among the non-responders, the decline also did not reach statistical significance from $.34$ to $.2438 \times 10^9/\text{L}$ ($p = .5$). The CRP was normal at baseline in most patients in both the responder (83 %, $n = 18$) and non-responder group (66.6 %, $n = 3$). The mean IgE level rose from 448 IU/mL at baseline ($n = 22$) to 822 IU/mL ($n = 18$) at week 16 and declined to 713 at week 52 ($n = 16$). Two patients did not have an IgE level taken at 52 weeks.

Tolerability, discontinuation and side effects

The total number of adverse effects reported as probably attributable to the drug, was 16. 10 % of patients had an adverse event as shown in Table 3. At week 12, treatment was stopped in one patient due to shoulder arthralgia. The drug was stopped in a further two patients at week 16 due to treatment ineffectiveness. These patients did not have any symptomatic improvement during this time interval with ACT score at week 0 being 7 and 5 and repeat at week 16 being 7 and 11 respectively. At week 20, treatment was stopped in another patient in view of worsening intolerable arthralgias of his hands. There were 12 (55 %) patients who had no adverse drug reactions. There were no reports on death or anaphylaxis or diagnosis of malignancy.

Fig. 1 Comparison of Asthma Control Test (ACT) score at weeks 0 (n = 22), 16 (n = 22), 32 (n = 18), 52 (n = 18)

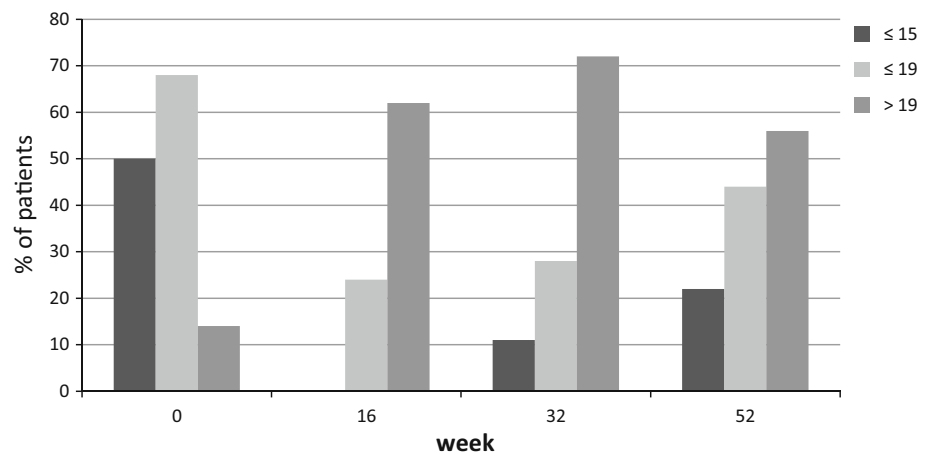


Fig. 2 Percentage of patients and their GETE at 16 (n = 21), 32 (n = 18) and 52 (n = 18) weeks of treatment

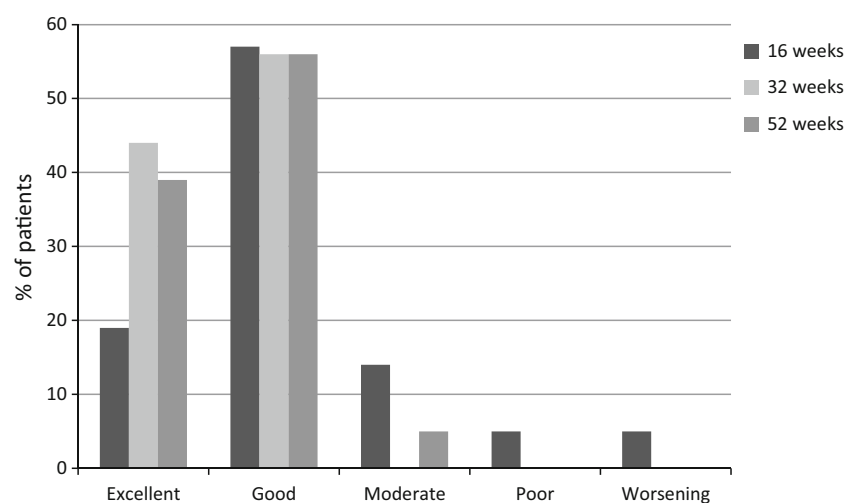


Table 2 The effect of omalizumab on clinical outcomes in the responder group (n = 18)

Weeks	0 Total no.	0 Mean	52 Total no.	52 Mean	% Change	p value	95 % CI
Number of exacerbations	76	4.2	48	2.6	−36.8	.03	−.58 to 3.7
Hospitalizations	5	.28	3	.17	−40	.6	−.3 to .48
Number of days off work	89	4.9	19	1	−79	.09	−1.77 to 9.55
Unscheduled health care visits	389	21.6	125	6.9	−67	.2	20.63 to 49.95
OCS courses	58	3.2	22	1.2	−62	.003	1.2 to 4.38

The bold figures are the ones which are statistically significant

Cost related to healthcare resource utilisation and days off work

Total costs related to asthma hospital-stay and medicines administered during hospitalisations in this patients' cohort were 14,402.68 euro for the 52 weeks prior to omalizumab treatment. Five patients required hospitalisation ranging from a 3 day stay to 28 days. Costs decreased to 4,417.61 euro, resulting from three patient hospitalisations ranging

from 3 to 6 days, following 1 year on omalizumab. Costs for prednisolone courses during the year ranged from 5.80 euro prior to commencing omalizumab to 2.20 euro following omalizumab. Cost for unscheduled doctor visits were three times as much in the year prior to starting omalizumab (3,890 euro), with all patients except six having an unscheduled doctor visit at least once. Cost for unscheduled doctor visits for the year following omalizumab were 1,250 euro, with six patients requiring such

Table 3 Adverse events experienced with omalizumab therapy (n = 22)

Adverse events	n (%)	Discontinuation of treatment
Headache	4 (18)	No
Injection site reaction	2 (9)	No
Myalgias	2 (9)	No
Lethargy	2 (9)	No
Nausea	2 (9)	No
Dizziness	1 (4.5)	No
Weight gain	1 (4.5)	No
Arthralgias	2 (9)	Yes (weeks 12, 20)
Nasopharyngitis	1 (4.5)	No

visits. The indirect costs related to days offwork, resulting from four patients of the full cohort, amounted to 3,889.30 euro prior to commencing omalizumab. These cost decreased by almost 80 % to amount 830.30 euro, with three patients requiring sick leave. The total annual cost for omalizumab in the cohort of patients who had omalizumab for 52 weeks amounted to 295,935.12 euro.

The results of cost analysis indicates that administration of omalizumab decreases the costs related to hospital stay, to unscheduled care visits and to number of days off work, but this has not been analysed further.

Efficacy and tolerability of omalizumab in patients requiring out-of-range doses from those recommended by the SmPC [20]

Five adult patients (three males/two females) had an IgE level or weight which is not included in the SmPC's omalizumab dosing table. IgE level ranged from 926 to 3,020 IU/ml with patients' weight ranging from 51 to 120 kg. The maximum dose of omalizumab (600 mg every 2 weeks) was prescribed. One out of five patients discontinued omalizumab due to clinical inefficacy at week 16. Another patient had the dose reduced at week 12 due to myalgias, which persisted despite dose reduction. Omalizumab was thus stopped at week 16. The other three patients had a decrease in the number of hospitalisations (3 vs 0), exacerbations (5 vs 1), unscheduled healthcare visits (3 vs 0) and days off work (50 vs 0) and an improvement in the mean ACT score (17 vs 23) 52-weeks post omalizumab initiation. None of these three patients suffered any adverse events.

Discussion

Preliminary NICE appraisal did not recommend omalizumab within its marketing authorisation for treating severe persistent allergic asthma since current benefits did

not lower incremental cost-effectiveness ratios to acceptable levels [27]. The final appraisal acknowledged the “uncaptured benefits of reducing dependence on oral corticosteroids” and concluded that these were sufficient to justify accepting an increase in cost per QALY gained [28]. Results of effectiveness presented by Molimard et al. [29] suggested that the efficacy demonstrated in randomised controlled trials can be extrapolated to a real-life setting. However, evidence based treatment decisions are sometimes based on studies which include a very small and highly selected proportion of the patient population. Therefore, it is questionable whether data from evidence based studies can be extrapolated to a larger ‘real life’ population of patients [30].

One key finding of this study was the significant reduction in the number of asthma exacerbations. However, the margin of exacerbation reduction was higher in other studies with Cazzola et al. 79 % reduction [14], Vieira et al. 70.1 % reduction ($p = .002$) [31], Brussels et al. 66 % reduction ($p < .001$) [12], Tzortzaki et al. 65 % ($p = .0002$) reduction [32], and 62 % reduction in the study by Molimard et al. These studies were all non-randomised, non-controlled trials and the sample sizes varied between the studies (22 patients in our study) compared to 14 patients in the study by Vieira et al. [31], 66 patients—Tzortzaki et al. [32], 142 patients—Cazzola et al. [14], 147 patients—Molimard et al. [29] and 158 patients—Brussels et al. [12].

The significant reduction in asthma exacerbations has transmitted into a reduction in the number of hospitalisations, unscheduled doctor visits and days off work; however, at 52 weeks, reduction in these outcomes was non-significant. There is an inconsistency in these findings amongst studies. Brussels et al. [12] observed a decreasing trend in hospitalisations but they failed to reach a significant improvement. A small study ($n = 33$) in Israel [18] also failed to demonstrate a significant hospitalisation reduction over a 1-year period (with 9 vs 6 admissions in the year pre- and post- omalizumab initiation ($p > .52$ but a significant decrease in the number of emergency room visits ($p < .05$)). Korn et al. [13], over a 6-month period showed a significant reduction of 77.5 % ($p < .001$) in asthma-related hospitalisations, and an 80.8 % reduction ($p < .001$) in unscheduled healthcare and emergency room visits.

An improvement in the ACT score at 16 weeks was maintained at 52 weeks, also significant in other studies [31, 32], which demonstrated sustained improvement at 2 years ($p = .008$) [31] and 4 years ($p < .0001$) [32]. The response to omalizumab measured with the GETE scale rated as good to excellent in 76 % at 16 weeks and 95 % at week 52, as compared to other studies which rated good to excellent in 77 % of patients [14].

Another significant finding was the decrease in OCS use, which is also supported by findings of other studies [14, 18]. Reduction in the use of OCS can have an indirect benefit in terms of long-term management of side effects. Even though feeling subjectively better, four patients found it difficult to decrease the dose or terminate the drug, suggesting an element of psychological dependence.

This study failed to show a significant improvement in average FEV₁, as opposed to other studies [11, 31–33]. There was a 63.4 % improvement in lung function after 4 months and a 65.1 % improvement at 6 months in the study by Korn et al. [13]. Vieira et al. [31] showed a significant rise in FEV₁ from baseline (51.7 ± 12.3 to 57.4 ± 18.2 % at 16 weeks, $p = .041$; 55.6 ± 15.7 % at 1 year, $p = .007$ and 65.0 ± 12.0 % at 2 years, $p = .007$). Menzella et al. [33] demonstrated FEV₁ at 4 years at 75.3 %, with a net increase ($p = .009$) compared with baseline FEV₁ values (58.6 %). An increase of 10.1 % in FEV₁ ($p < .05$) was shown in another study [11].

Omalizumab had a favourable safety profile with arthralgia being the only intolerable adverse event. Frequency and type of adverse events were similar to other studies [13, 29, 32]. Arthralgia was not the cause of discontinuation in the study by Tzortzaki et al. [32] but was considered as a serious adverse event in another study [29] and was the reason for discontinuation in a patient in another [31].

Our findings should be interpreted with caution due to the small sample size and its observational open-label nature. Though not adequately powered, it gives a global result of the Maltese population. A multi-national study would be ideal to compare to European data. Since evaluation of quality of life (QOL) was not assessed, the use of a validated QOL tool would clarify the decision on treatment responsiveness. Moreover, confounding factors such as the placebo effect and adherence to asthma treatment due to more frequent doctor visits, were not taken into account, also a limitation in other studies [29].

Conclusion

This “real-life” prospective study shows that omalizumab had an acceptable safety profile and was well tolerated. The response rate was 86 % at week 16 and 82 % at week 52. The addition of omalizumab to maximal therapy resulted in significant reductions in number of asthma exacerbations, OCS courses required as well as the ACT score. There was no significant improvement in FEV₁, hospitalizations, unscheduled health care visits and number of days off work. Our experience shows that even with smaller effects on FEV₁, patients have subjective improvement in their asthma-related symptoms. Further evaluation of our cohort

will provide us with effectiveness and tolerability of treatment in the long term.

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Conflicts of interest None.

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