Campisi et al. World Allergy Organization Journal (2020) 13:100103
http://doi.org/10.1016/j.waojou.2020.100103

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Adherence to omalizumab: A multicenter "real-world" study

Raffaele Campisi[a], Claudia Crimi[a]*, Rossella Intravaia[b], Simona Strano[b], Alberto Noto[c], Maria Pia Foschino[d], Giuseppe Valenti[e], Vittorio Viviano[e], Corrado Pelaia[f], Luisa Ricciardi[g], Nicola Scichilone[h] and Nunzio Crimi[b]

ABSTRACT

Background: Adherence to medications is crucial in patients with severe asthma in light of the negative clinical impact and costs of non-adherence. Adherence to omalizumab has not been well studied in real-world settings. The aim of this study was to assess adherence to omalizumab and evaluate treatment effectiveness in relation to adherence.

Methods: This was a retrospective, observational, and multicenter real-world study. Omalizumab dose, timing of administration, and duration of treatment ($<$2 years; 2–4 years; $>$ 4 years) were analyzed. Adherence was evaluated by examining rates of expected and missing doses. Good adherence ($<$10% of doses missed) and poor adherence ($>$10% doses missed) were determined. For effectiveness in relation to adherence of omalizumab we considered asthma exacerbations, hospitalizations, asthma control test (ACT), and Forced Expiratory Volume in 1 s (FEV_1).

Results: A total of 196 patients were evaluated, and 161 were suitable for data analyses. Good adherence was shown in 90.7% of patients and poor adherence in 9.3%. Considering adherence in relation to treatment duration: $<$2 years, 87.8% of patients were adherent (expected doses, 1186; missed doses, 53); 2–4 years, 85.9% were adherent (expected doses, 2985; missed doses, 127); $>$4 years, 100% were adherent (expected doses, 6120; missed doses, none). Indices of efficacy between pre- and post-treatment showed significant improvement ($p < 0.001$). The effectiveness indices between pre- and post-treatment, among adherent and non-adherent patients, ACT, and asthma exacerbations both showed significant differences ($p = 0.043$ and $p = 0.049$, respectively). Binomial logistic regression analysis showed that increasing age, better ACT score, and 14-day timing were significantly associated with increased adherence to therapy.

Conclusions: High adherence to omalizumab was demonstrated in a real-world setting, which was associated with better outcomes and control of asthma.

Keywords: Severe asthma, Omalizumab, Adherence, Efficacy, Real-world

[a]Respiratory Medicine Unit, A.O.U. "Policlinico-Vittorio Emanuele", Catania, Italy
*Corresponding author. Respiratory Medicine Unit A.O.U. "Policlinico-Vittorio Emanuele" Via S. Sofia, 78 ,95123 Catania, Italy. E-mail: dott.claudiacrimi@gmail.com
Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2020.100103

Received 11 July 2019; Received in revised from 13 December 2019; Accepted 23 December 2019

INTRODUCTION

Adherence to prescribed medications is defined as the extent to which medicines are taken as directed by physicians and the degree to which health-related behaviors are followed.[1] When managing chronic diseases, adherence to essential long-term therapies is an important factor. Non-adherence interferes with the success of treatment and has serious consequences, often resulting in poor health outcomes and increasing healthcare expenses; unfortunately, non-adherence is common among patients with asthma.[1,2] In fact, it is well known that the appropriate use of asthma controller medication reduces morbidity and mortality and also improves quality of life, but adherence tends to be poor in about one-half of patients.[2,3] Barriers to adherence in patients with asthma are various and complex.[3,4] As with other diseases, these include patients' concerns such as fear of immediate and long-term side effects, psychological problems and depression, forgetfulness, inadequate follow-up, poor perception of disease, inadequate physician-patient relationships, and excessive treatment complexity, as well as costs.[4,5] Furthermore, non-adherence also implies other undesirable patient behavior, including not attending regular follow-up visits and even self-discharge from hospital before recovery.[6] In addition, treatment discontinuation is one of the most relevant aspects of adherence, and drop-out rates have been shown to serve as surrogate marker of drug adherence.[3]

Recently, monoclonal antibodies were introduced for the treatment of severe uncontrolled asthma; the first biological agent to emerge for clinical use was omalizumab, which is indicated as add-on therapy for severe persistent allergic asthma refractory to high dose inhaled corticosteroids and long-acting beta 2 –agonists (ICS/LABA). The efficacy and safety of omalizumab have been clearly demonstrated in several randomized clinical trials (RCTs) and real-life studies.[7–11] However, adherence to omalizumab in real-world settings has not been well characterized. Reported estimates of adherence to omalizumab in the literature vary from 43% to 70%.[5,12,13] In the study by Broder et al. adherence rates at 1 year were superior to fluticasone/salmeterol in a managed care population, with 54% of users adherent at one year compared to 19% with fluticasone/salmeterol.[5] Other analyses have suggested that a 4-week dosing regimen may be preferred and give better adherence than a 2-week regimen, although it was suggested that adherence may be complex and related to several factors such as age and lung function.[12] Even if there is no consensus on the definition of adequate adherence at present,[1] overall adherence can be considered to be inadequate. Despite this, omalizumab can be considered to be essential for adequate management of patients with severe asthma.[6] Moreover, reports of long-term outcomes of biological therapies for severe asthma, outside clinical trials, are limited.[1]

Thus, given the limited information on adherence to omalizumab therapy, the aims of the present study were to: (1) evaluate real-world adherence to omalizumab; (2) verify the correlation between effectiveness of omalizumab and patient adherence; (3) assess adherence to other asthma controller therapies such as ICS/LABA in patients undergoing treatment with omalizumab; and (4) assess associations between patients' demographic and clinical characteristics and adherence.

MATERIALS AND METHODS

Study design and sources of data

This was a retrospective, observational multicenter study examining real-world treatment scenarios of 196 patients with severe persistent allergic asthma. We retrospectively reviewed data of all severe asthma patients who were treated with omalizumab for at least 12 months in 6 specialized outpatient facilities in Italy: (1) Respiratory Medicine Unit - A.O.U. "Policlinico-Vittorio Emanuele", Catania; (2) Respiratory Medicine Unit - A.O.U. "Policlinico Giaccone, Palermo; (3) Allergy and Clinical Immunology Unit - A.O.U "Policlinico G. Martino, Messina; (4) Allergy and Pulmonary Unit - Center for Severe Asthma - ASP Palermo; (5) Pulmonary Unit - A.O.U. "Mater Domini", Catanzaro; and (6) Institute of Respiratory Diseases, Azienda Ospedaliero Universitaria di Foggia.

Patient population

We considered all adult patients diagnosed with severe asthma (defined as at least 2 documented

exacerbations, hospitalization, and night-time symptoms, requiring Step 4 or 5 treatment to achieve control; or asthma that remained uncontrolled despite such treatment, as specified in the GINA 2018 report[14]) who met all clinical indications and therapeutic criteria for omalizumab treatment (total serum IgE of 30–1500 IU/ml; documented sensitization to at least one perennial allergen detected by prick test or serum specific IgE) and who were continuously treated with omalizumab for at least 1 year, between 2008 and 2018. Patients with other respiratory diseases that may share common clinical manifestations of severe asthma (i.e. acute bronchopulmonary aspergillosis, vasculitis) were excluded. This study adhered to the Declaration of Helsinki and received approval from the Ethics Committee "Catania 1" at Policlinico Hospital (Protocol Number 138/2018/PO).

Data collection

An established database of relevant variables was accessed for data analysis. All patients involved in the study had continued omalizumab treatment for at least 1 year. Data on treatment drop-outs (35 patients) were also collected. Demographics (age, sex) and baseline asthmatic profiles (age at onset, sensitization to perennial aeroallergens, total IgE level, baseline, and post-bronchodilation Forced Expiratory Volume in 1 s (FEV_1), asthma exacerbation/hospitalization prior to omalizumab administration, and maintenance therapies were retrieved.

Assessment of omalizumab adherence

Data on omalizumab dosage, timing of administration (2 weeks vs. 4 weeks), and duration of treatment were analyzed. Patients were arbitrarily divided into 3 groups based on duration of omalizumab treatment: (1) $<$ 2 years, (2) 2–4 years, and (3) $>$ 4 years. Individual doses of omalizumab and timing were determined via a dosing table, based on each patient's IgE level. Data on treatment adherence, delay, and discontinuation to scheduled timing of prescriptions were collected for each patient. Adherence to omalizumab was assessed by examining rates of medication access (expected and actual) and missing doses, as well as duration of treatment. Patients were subdivided into 2 subgroups based on the proportion of missing doses: good adherence was considered in patients missing $<$10% of scheduled doses, as previously reported,[12] and poor adherence was considered arbitrary in those missing $\geq$10% of planned doses.

Assessment of omalizumab effectiveness

The effectiveness of omalizumab treatment was evaluated in relation to: (1) frequency of asthma exacerbations; (2) total hospitalizations; (3) level of asthma control; and (4) improvement of FEV_1. Severe asthma exacerbations were defined as worsening of asthma symptoms requiring systemic corticosteroids. Levels of asthma control were assessed pre- and post-treatment using the 5-point scoring system of the Asthma Control Test (ACT).[15] An overall score of at least 20 corresponds with well-controlled asthma, whereas a score $\leq$19 reflects poor control. The minimally clinical important difference (MID) for the ACT score was also considered.[15]

Adherence to inhaler therapy

To investigate adherence to inhaler therapy during omalizumab treatment, the medication possession ratio (MPR) of ICS/LABA therapy received during the past year of treatment with omalizumab was obtained for each patient. MPR denotes the proportion of days in observational periods that individuals are in possession of required medications. MPRs from 0 to 50% are indicative of low adherence; 50–80% good adherence; and $>$80% high-level adherence.[16]

Statistical analysis

Descriptive statistics for the study population were derived from mean values and standard deviation (SD) or 95% confidence intervals (CI) for continuous variables, median, and interquartile range (IRQ) for non-normally distributed variables, and numbers and percentages for categorical variables. The normality of data distribution was checked using the Shapiro-Wilk test. To assess the efficacy of omalizumab treatment, we analyzed different outcome variables (ACT, FEV_1, asthma exacerbations, hospital admission) before and after treatment with a non-parametric test (Wilcoxon signed-rank). Binomial logistic regression analysis was performed to investigate the effects of age, gender, baseline ACT, ACT after therapy, and

timing of prescription on the likelihood of adherence >90%. Data were analyzed using SPSS version 18 software (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

RESULTS

Patient demographics and clinical characteristics

In this retrospective, observational analysis, 196 patients with a diagnosis of severe persistent asthma and who were treated with omalizumab for at least 1 year were included. Of the 196 patients, 35 (17.8%) discontinued treatment (drop-out) and were not considered for data analysis. Thus, 161 patients with severe persistent, poorly controlled asthma who continued treatment with omalizumab until the data analysis were included.

Demographic and clinical characteristics of the study population are summarized in Table 1. Patients had a mean age of 55.2 ± 12.3 years; 40.4% were male and 59.6% female; mean pre-bronchodilator FEV_1 was 60% ± 10% of predicted; mean duration of asthma from initial diagnosis was 26.9 ± 13.2 years. The median total IgE prior to treatment with omalizumab was 395 (IQR 456) IU/ml. In the 12 months prior to omalizumab treatment, 41 (25.5%) patients required oral corticosteroids (OCS) for asthma exacerbation. The median number of asthma exacerbations per year was 7 (IQR = 8), and the median ACT score was 12 (IQR = 6), indicating poorly controlled asthma.

Total population	N = 161
Age, years, mean (SD)	55.2 (12.3)
Sex, n (%)	
Male	65 (40.4)
Female	96 (59.6)
Duration of asthma,years, mean (SD)	26.9 (13.2)
Total serum IgE level, UI/ml, median (IQR)	395 (456)
Positive skin prick test, n (%)	161 (100)
ICS plus LABA, n (%)	161 (100)
Patients requiring OCS for asthma exacerbation in the 12 months before omalizumab, n (%)	41 (25.5)
ACT score, median (IQR)	12 (6)
FEV_1, %, mean (SD)	60 (10)
Number of asthma exacerbations/year, median (IQR)	7 (8)
Number of hospitalizations/year, mean (SD)	1.9 (3)
Delays of administration, n (%)	43/161 (26.7)
Omalizumab treatment regimen	
Every 2 weeks, n (%)	53 (32.9)
Every 4 weeks, n (%)	108 (67.1)
Duration of treatment	
>1−≤2 years, n (%)	49 (30.4)
>2−≤4 years, n (%)	64 (39.8)
>4 years, n (%)	48 (29.8)

Table 1. Baseline demographic and clinical characteristics of patients

Regarding posology, 53 patients (32.9%) received the treatment every 2 weeks and 108 patients (67.1%) were treated every 4 weeks. Forty-nine patients (30.4%) had been treated for 1–2 years, 64 (39.8%) for 2–4 years, and 48 (29.8%) for > 4 years.

Drop-outs

Reasons and timing of drop-out are shown in Table 2. Of the 35 patients who dropped out of treatment, 14 (40%) discontinued after 1 year, 9 (25.7%) after 2 years, 4 (11.4%) after 3 years, and 8 (22.9%) after 4 years. Considering all patients who discontinued treatment with omalizumab, 19 (54.3%) stopped the treatment for subjectively perceived lack of efficacy; 11 (31.4%) for personal decisions (logistical and organizational problems); 1 (2.8%) for an adverse event (skin rush at the site of injection); and 4 (11.4%) for reasons other than an adverse event (diagnosis of different pathology).

Effectiveness of omalizumab treatment

Indices of the effectiveness of omalizumab treatment are shown in Table 3. Asthma exacerbations/year, hospitalizations/year, FEV1, and ACT score between pre- and post-treatment were all significantly improved ($p < 0.001$). Asthma exacerbations decreased from 10.1 (95% CI = 7.5 to 12.6) pre-treatment to 1.0 (95% CI = 0.7 to 1.3) post-treatment; there were 1.8 (95% CI = 1.2 to 2.4) hospitalizations before treatment compared to 0.1 (95% CI = 0 to 0.2) after treatment; FEV_1 improved from 60% (95% CI = 57%–62%) before treatment to 71% (95%CI = 69%–73%); the ACT score increased from 13.3 (95% CI = 12.6 to 14.1) pre-treatment to 20.2 after treatment (95% CI = 19.5 to 20.9).

When the cohort was divided into 3 groups in relation to treatment duration, we observed a significant improvement in the delta ACT score (before and after omalizumab treatment) that progressively and significantly increased with duration of the treatment (Table 4). This suggests that omalizumab improves the ACT score and that this improvement is always greater than the ACT MID, independently of the number of years of treatment. No significant differences in delta ACT were found considering the timing of administration of omalizumab (2 weeks delta ACT 7.6, 95% CI = 6.7 to 8.4 vs. 4 weeks delta ACT 7.5, 95% CI = 6.3 to 8.8; $p = 0.92$). Likewise, hospitalizations significantly decreased over time of treatment in relation to treatment duration (Table 4). The rate of exacerbations decreased rapidly (in less than 2 years) after initiation of treatment, but no significant reduction was seen with increased years of treatment ($p = 0.11$; Table 4). After initial improvement, no changes

Total drop-outs, n (%)	35 (17.8)
Patient decision	11 (31.4)
Lack of efficacy	19 (54.3)
Adverse events	1 (2.8)
Other causes	4 (11.4)
Timing of drop-out, n (%)	
1st year	14 (40)
2nd year	9 (25.7)
3rd year	4 (11.4)
>4th year	8 (22.8)

Table 2. Reasons and timing for drop-out

		P value
ACT score mean (95% CI)		
Pre-treatment	13.3 (12.6–14.1)	
Post-treatment	20.2 (19.5–20.9)	<0.001
FEV_1% mean (95% CI)		
Pre-treatment	60 (57–62)	
Post-treatment	71 (69–73)	<0.001
Asthma exacerbations/year, mean (95% CI)		
Pre-treatment	10.1 (7.5–12.6)	
Post-treatment	1.0 (0.7–1.3)	<0.001
Hospitalizations/year, mean (95% CI)		
Pre-treatment	1.8 (1.2–2.4)	
Post-treatment	0.1 (0–0.2)	<0.001

Table 3. Indices of omalizumab effectiveness pre- and post-treatment

were seen in FEV_1 at longer treatment duration (p = 0.11; Table 4).

Adherence to omalizumab treatment

Considering all patients treated with omalizumab, good adherence (missing <10% of doses) was seen in 90.7% and poor adherence (missing >10% of doses) in 9.3%. No significant differences in adherence were found between patients treated every 2 weeks vs. every 4 weeks (98.9%, 95% CI = 97.7 to 100 vs. 94.9%, 95% CI = 92.9 to 96.9; p = 0.8). Adherence in relation to duration of treatment was very high between groups. Among those on treatment <2 years (n = 49, 30.4%), good adherence was found in 87.8% of patients and poor adherence in only 12.2%; considering 1186 expected doses, only 53 (4.5%) were missed. Among those on therapy for 2–4 years (n = 64, 39.8%), good adherence was seen in 85.9% of patients and 14.1% were poorly adherent; only 127 (4.2%) doses were missed considering 2985 expected doses. For those on therapy for >4 years (n = 48, 29.8%), good adherence was shown in 100% of patients; no missed doses were detected among the 6120 expected.

Delay of omalizumab administration was registered in 43 of 161 patients (26.7%); 13 (8%) for work/study reasons, 4 (2%) for family reasons, 3 (1%) for asthma exacerbation, 7 (4%) for health reasons not related to asthma, 11 (6%) for logistics reasons, 5 (3%) for forgotten dose. The presence of asthma symptoms in relation to delayed administration was shown in 19 patients (44.2%). Among patients with good adherence, only 12 (27.3%) showed symptoms of asthma. Considering asthma-related outcomes in relation to omalizumab adherence, a significant difference between pre- and post-treatment was demonstrated only for ACT (p = 0.043) and asthma exacerbations (p = 0.049) between highly adherent (>90%) and poorly adherent (<90%) patients (Table 5).

Delta, mean (95%CI)	<2 years	2–4 years	>4 years	P value
ACT	6.4 (5–7)	7.2 (6–8)	9.3 (8–10)	0.007
Exacerbations	−10.3 (−14– −7)	−13.2 (−18– −8)	−12 (−16– −8)	0.11
Hospitalizations	−1.1 (-2 - 0)	−2.1 (-3 - 1)	−4.3 (-14 - 5)	0.04
FEV_1	0.1 (0–0.2)	0.1 (0–0.2)	0.1 (0–0.1)	0.11

Table 4. Changes (delta between pre- and post-treatment) in ACT, exacerbations, hospitalizations and FEV_1 at various times after initiating omalizumab

Delta, mean (95%CI)	Adherence <90%	Adherence >90%	P value
ACT	5.7 (3.5–7.9)	7.7 (7.0–8.5)	0.043
FEV_1%	0.05 (0.005–0.1)	0.1 (0.1–0.14)	0.07
Exacerbations	−8.6 (−17.0 - 0.2)	−12 (−15.0–−9.5)	0.049
Hospitalizations	−0.6 (−1.3 - 0.05)	−2 (−2.5–−1.3)	0.14

Table 5. Changes (delta between pre- and post-treatment) in indices of effectiveness among adherent and non-adherent patients

Adherence to ICS/LABA therapy and medication possession ratio

A high level of adherence to ICS/LABA therapy was found in patients with high adherence to omalizumab (missing <10% of doses). Only 24 (14.9%) patients were non-adherent to ICS/LABA vs. 119 (73.9%) who continued the inhalers. Among patients with poor adherence to omalizumab treatment (missing >10% of doses) only 7 (4.3%) discontinued inhaler therapy vs. 8 (4.9%) who continued the prescribed inhalers regimen. High adherence to ICS/LABA treatment was further confirmed by the MPR. Both highly (n = 121, 82.9%) and poorly (n = 14, 93.3%) adherent to omalizumab had high adherence to ICS/LABA according to MPR.

Binomial logistic regression analysis

The logistic regression model was statistically significant (χ^2 (5) = 16.338, p < 0.001). The model explained 23% (Nagelkerke R^2) of the variance in adherence and correctly classified 89% of cases. The sensitivity was 99% with a specificity of 7%. Of the five predictor variables, only three were statistically significant: age, ACT after therapy and timing (Table 6). Thus, increasing age, better ACT score, and 14-day timing were associated with an increased likelihood of adherence to therapy.

DISCUSSION

The main findings of our study can be summarized as follows: (1) adherence to omalizumab treatment is very high in real-world settings, regardless of dosing frequency; (2) omalizumab is very effective in the management of patients with severe asthma, improving asthma-related outcomes, with sustained benefits in the long-term; (3) adherence to inhaled ICS/LABA remains high in the highly selected population of severe asthmatic patients on omalizumab treatment; and (4) older age, better ACT score, and 14-day timing were associated with increased to adherence to therapy.

To the best of our knowledge, the present study is the most updated evidence on adherence to omalizumab in a real-world clinical setting, with

	B	S.E.	Wald	gl	P value	Odds Ratio	95% CI
Age	0.051	0.025	4.138	1	0.042	1.052	1.002–1.105
Gender (male)	0.230	0.625	0.135	1	0.713	1.258	0.369–4.286
Baseline ACT	−0.075	0.097	0.606	1	0.436	0.928	0.768–1.121
ACT	0.194	0.095	4.167	1	0.041	1.214	1.008–1.463
Timing (14 vs 28 days)	2.468	1.109	4.950	1	0.026	11.794	1.341–103.705
Constant	−3.967	2.188	3.287	1	0.070	0.019	

Table 6. Binomial logistic regression analysis to investigate the effects of selected variables on likelihood of adherence >90%

30% of patients treated for more than 4 years, which is the longest follow-up time reported to date in Italy. Indeed, good adherence to omalizumab, defined as missing <10% of scheduled doses, was maintained by >90% of patients regardless of the dose frequency regimen; moreover, excellent long-term adherence was seen after 4 years of prescribed monoclonal therapy, with 100% of patients remaining on treatment. These results could be due to a two-way relationship between adherence and efficacy, wherein good efficacy favors good adherence to therapy. Obviously, adherence to omalizumab treatment enhances all beneficial outcomes of efficacy such as control of asthma, reduction of exacerbations and hospitalizations, and improvement of FEV_1; moreover, the improvement of the above asthma-related outcomes achieved with omalizumab treatment might be strengthened, in turn, by adherence to therapy. Nevertheless, all outpatients who received omalizumab biweekly or every 4 weeks in hospital settings had regular follow-up consultations with chest physicians; this may have acted as a behavioral strategy and could have further improved adherence and positive beliefs about treatment, as previously demonstrated in other studies.[12,17,18] In contrast with previously published studies,[12] patients who were administered omalizumab every 4 weeks were as adherent as those who received the drug every 2 weeks (94.9% vs. 98.9%; $p = 0.16$). Herein, improved adherence was associated with 14-day timing. It is possible that the above results are related to the regular follow-up of each patient with his/her clinician.

Our results also demonstrate that omalizumab improves the delta ACT score and that this improvement is greater than the ACT MID, which increases with duration of treatment. Of note, the positive relationship between better ACT score and age with adherence was also demonstrated by logistic regression analysis. In addition, hospitalizations significantly decreased with increased time of treatment. This is an important finding, since the optimal duration of treatment with omalizumab has not been established, and few reports from real-life studies have described effectiveness outcomes up to and exceeding 52 weeks.[9,19–23] Interestingly, our study showed that even patients who are not fully adherent to omalizumab had a significant decrease in the risk of exacerbation; we can speculate that this is due to the powerful effect of omalizumab and that missing some doses does not affect the control of asthma.

There is limited information on adherence to omalizumab and inhaler drugs (ICS/LABA). A retrospective study evaluating persistence and adherence >1 year was the first to compare adherence to omalizumab in new users vs. inhaled medications.[5] Mean adherence was 64.6%, more than twice that achieved with a once-daily fixed dose combination with ICS/LABA.[5] In our study, high adherence to omalizumab paralleled with high adherence to ICS/LABA therapy. These results are in contrast with previous studies in which adherence to the ICS/LABA therapy in asthmatic patients is poor.[24] This can be explained by the fact that maximal inhalation therapy is required to start treatment with omalizumab, and the significant benefits derived from it can result in greater adherence to ICS/LABA. Furthermore, close outpatient follow-up may have also contributed to better adherence.

A retrospective study reported that the 12-month adherence rate for omalizumab (defined as ≥ 80% of days covered) was 43%.[13] Caminati and coworkers also reviewed drop-out rates in real-life studies and in randomized controlled trials (RCTs), reporting a drop-out rate ranging from 0 to 45.5%, with lack of efficacy or patient preference typically cited as the reason for discontinuation.[2] In RCTs with omalizumab, the drop-out rate ranged from 7.1 to 19.4%, primarily due to patient preference or adverse events. In another study, Janson and coworkers evaluated adherence to omalizumab during a 5-year period, examining the rate of missed doses and distribution of patient adherence (good vs poor).[12] Good adherence (defined as rate of missed dose <10%) was observed in 55.9% of patients treated biweekly, and in 62.6% of patients treated every 4 weeks. High adherence rates in outpatient settings were also observed by Canonica et al. during 12-month follow-up in an observational, two-phase study, in which the majority of patients continued omalizumab treatment during the entire observation period.[25]

Overall, omalizumab has been associated with favorable effectiveness and safety outcomes.

Long-term omalizumab administration improves asthma outcomes in real-life setting such as exacerbations, hospitalizations, nocturnal symptoms, and ACT scores, with no adverse impact on risks of side effects.[26-30]

In agreement with published data, our observational study showed that patients experienced significant reduction in asthma exacerbations, fewer hospitalizations, improvement in pulmonary function (FEV_1), and ACT score compared with the 12 months before treatment ($p < 0.001$ for all). Herein, a large proportion of patients who demonstrated good adherence achieved significant improvement of MIDs (always > 3) after the first year of treatment. Moreover, in patients treated for >4 years, the improvement of MIDs was >9. This result is consistent with data reported by other studies.[31,32]

Considering the reasons for discontinuation in the present series, only one patient had an adverse event (skin rush at the site of injection), thus confirming the good safety profile of omalizumab, as demonstrated in previous studies.[29] The main strength of our study is that our data are extended beyond 4 years of omalizumab treatment in 30% of the study population; moreover, the size of the study population is also relatively large considering the study duration. The major limitation of this study is its retrospective design.

In conclusion, adherence to omalizumab in patients with asthma was high in our series, and was further associated with older age and better ACT score. Adherence was independent of the frequency of treatment and did not affect the effectiveness of treatment. Indeed, there was a sustained benefit of omalizumab in terms of improvement of both ACT and FEV_1, as well as a reduction in exacerbations and hospitalizations in relation to duration of treatment.

Ethics approval and consent to participate
The study received approval from the Ethics Committee "Catania 1" of Azienda Ospedaliera Policlinico-Vittorio Emanuele di Catania (Protocol Number 138/2018/PO) with written informed consent obtained from each participant.

Authors' contributions
NC, CC, and RC designed the study. RI, SS, MPF, GV, VV, CP, LR, NS contributed to the clinical and laboratory work for the study. RI and SS contributed to data collection. AN contributed to data analysis. RC, CC, and NC drafted the article and revised it critically for important intellectual content. RC, CC, and NC contributed to final approval of the version to be published. All authors contributed to drafting, revising and editing the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Submission declaration
The work has not been published or submitted to another scientific journal and is not being considered for publication elsewhere. This submission represents original work and is approved by all authors.

Consent for publication
Not applicable.

Availability of data and material
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding
Not applicable.

Declaration of Competing Interest
All the authors declare no competing interests.

Acknowledgements
Raffaele Campisi and Claudia Crimi are co-first authors for this work. Editorial assistance for the manuscript was provided by Health Publishing & Services SrL and supported by Novartis Farma spa, Via Largo Umberto Biccioni, 1, Origgio, Varese, Italy.

Author details
[a]Respiratory Medicine Unit, A.O.U. "Policlinico-Vittorio Emanuele", Catania, Italy. [b]Respiratory Medicine Unit, A.O.U. "Policlinico-Vittorio Emanuele", Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy. [c]Anesthesia and Critical Care, A.O.U. Policlinico "G. Martino", Messina, Italy. [d]Department of Medical and Surgical Sciences, "Institute of Respiratory Diseases", Azienda Ospedaliero Universitaria di Foggia, Foggia, Italy. [e]Allergy and Pulmonary Unit - Center for Severe Asthma - ASP Palermo, Palermo, Italy. [f]Department of Medical and Surgical Sciences, University "Magna Graecia", Catanzaro Italy. [g]Allergy and Clinical Immunology Unit, A.O.U. Policlinico "G. Martino", Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy. [h]Department of Biomedicine and Internal and Specialistic Medicine (DIBIMIS), University of Palermo, Palermo, Italy.

REFERENCES

1. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–497.
2. Caminati M, Senna G, Stefanizzi G, et al. Drop-out rate among patients treated with omalizumab for severe asthma: literature review and real-life experience. *BMC Pulm Med*. 2016;16:128.
3. World Health Organization (WHO). Adherence to long-term therapies: evidence for action. Dis specific Rev. http://www.who.int/chp/knowledge/publications/adherence_section3.pdf. Accessed June 18, 2013.
4. Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin*. 2005;25:107–130.
5. Broder MS, Chang EY, Ory C, et al. Adherence and persistence with omalizumab and fluticasone/salmeterol within a managed care population. *Allergy Asthma Proc*. 2009;30:148–157.
6. Green RH, Shaw D. Strict adherence rules to obtain monoclonal therapy might cost lives. *Lancet Respir Med*. 2017;5:678–679.
7. Abraham I, Alhossan A, Lee CS, et al. Real-life' effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review. *Allergy*. 2016;71:593–610.
8. Cazzola M, Camiciottoli G, Bonavia M, et al. Italian real-life experience of omalizumab. *Respir Med*. 2010;104:1410–1416.
9. Lai T, Wang S, Xu Z, et al. Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis. *Sci Rep*. 2015;5:8191.
10. Molimard M, de Blay F, Didier A, et al. Effectiveness of omalizumab (Xolair) in the first patients treated in real-life practice in France. *Respir Med*. 2008;102:71–76.
11. Tzortzaki EG, Georgiou A, Kampas D, et al. Long-term omalizumab treatment in severe allergic asthma: the South-Eastern Mediterranean "real-life" experience. *Pulm Pharmacol Therapeut*. 2012;25:77–82.
12. Janson SL, Solari PG, Trzaskoma B, et al. Omalizumab adherence in an observational study of patients with moderate to severe allergic asthma. *Ann Allergy Asthma Immunol*. 2015;114:516–521.
13. Lafeuille MH, Gravel J, Zhang J, et al. Association between consistent omalizumab treatment and asthma control. *J Allergy Clin Immunol Pract*. 2013;1:51–57.
14. Global Initiative for Asthma (GINA). *GINA Report, Global Strategy for Asthma Management and Prevention*; 2018. http://www.ginasthma. Accessed March 24, 2019.
15. Schatz M, Kosinski M, Yarlas AS, et al. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol*. 2009;124:719–723 e1.
16. National Committee for Quality Assurance. HEDIS 2016 final NDC lists. Available from: http://www.ncqa.org/hedis-quality-measurement/hedis-measures/hedis- 2016/hedis-2016-ndc-license/hedis-2016-final-ndc-lists. Accessed February 2, 2020.
17. Gamble J, Stevenson M, Heaney LG. A study of a multi-level intervention to improve non-adherence in difficult to control asthma. *Respir Med*. 2011;105:1308–1315.
18. Sulaiman I, Greene G, MacHale E, et al. A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. *Eur Respir J*. 2018;51.
19. Bardelas J, Figliomeni M, Kianifard F, et al. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma*. 2012;49:144–152.
20. Barnes N, Menzies-Gow A, Mansur AH, et al. Effectiveness of omalizumab in severe allergic asthma: a retrospective UK real-world study. *J Asthma*. 2013;50:529–536.
21. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154:573–582.
22. Karpel J, Massanari M, Geba GP, et al. Effectiveness of omalizumab in reducing corticosteroid burden in patients with moderate to severe persistent allergic asthma. *Ann Allergy Asthma Immunol*. 2010;105:465–470.
23. Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest*. 2011;139:28–35.
24. Wu AC, Butler MG, Li L, et al. Primary adherence to controller medications for asthma is poor. *Ann Am Thorac Soc*. 2015;12:161–166.
25. Canonica GW, Rottoli P, Bucca C, et al. Improvement of patient-reported outcomes in severe allergic asthma by omalizumab treatment: the real life observational PROXIMA study. *World Allergy Organ J*. 2018;11:33.
26. Mansur AH, Srivastava S, Mitchell V, et al. Longterm clinical outcomes of omalizumab therapy in severe allergic asthma: study of efficacy and safety. *Respir Med*. 2017;124:36–43.
27. Di Bona D, Fiorino I, Taurino M, et al. Long-term "real-life" safety of omalizumab in patients with severe uncontrolled asthma: a nine-year study. *Respir Med*. 2017;130:55–60.
28. Korn S, Thielen A, Seyfried S, et al. Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany. *Respir Med*. 2009;103:1725–1731.
29. Braunstahl GJ, Chen CW, Maykut R, et al. The eXpeRience registry: the 'real-world' effectiveness of omalizumab in allergic asthma. *Respir Med*. 2013;107:1141–1151.
30. Casale TB, Luskin AT, Busse W, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from prospero, A prospective real-world study. *J Allergy Clin Immunol Pract*. 2019;7:156–164 e1.
31. Al-Ahmad M, Arifhodzic N, Nurkic J, et al. Real-life" efficacy and safety aspects of 4-year omalizumab treatment for asthma. *Med Princ Pract*. 2018;27:260–266.
32. Pelaia C, Calabrese C, Barbuto S, et al. Omalizumab lowers asthma exacerbations, oral corticosteroid intake and blood eosinophils: results of a 5-YEAR single-centre observational study. *Pulm Pharmacol Therapeut*. 2019;54:25–30.