

Long-term evaluation of response to omalizumab therapy in real life by a novel multimodular approach



The Real-life Effectiveness of Omalizumab Therapy (REALITY) study

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ABSTRACT

Background: The evidence on long-term real-life response measures to omalizumab therapy in moderate to severe asthma is limited. A universal assessment tool is needed to adequately evaluate response to omalizumab in these patients.

Objective: To design a multimodular response assessment tool and use it to measure and define response to omalizumab therapy in real-world settings.

Methods: The Real-life Effectiveness of Omalizumab Therapy (REALITY) study is a retrospective, long-term, real-life clinical study that evaluates response in individuals with allergic asthma who received omalizumab between 2004 and 2011. The Standardized Measure to Assess Response to Therapy (SMART) tool was designed to define response (1 year before to after treatment) by 3 modules: (1) physician's subjective assessment of asthma symptoms and control; (2) objective assessment of 6 parameters: improvement by 50% or more for asthma exacerbation, steroid bursts, emergency department visits, and hospitalizations; increase in forced expiratory volume in 1 second of 200 mL or greater; and improved Asthma Control Test score of 3 or higher; —and (3) true responders (patient meeting both module 1 and 2 criteria). Response was assessed and compared for 3 modules at desired time points.

Results: A total of 198 patients (mean age, 31.7 years [range, 3–77 years]; 98 [49%] female; mean omalizumab therapy duration, 2.49 years [range, 3 months to 8 years]; mean omalizumab dosage, 473 mg every 4 weeks; median baseline IgE level, 433 IU/mL) were included in this analysis. Overall visit adherence was 78%, although the adherence rate decreased annually by 20%. Response rates assessed by SMART modules were 61.3%, 60.8%, and 41.8% at 16 weeks, 84.8%, 72.2%, and 64.6% at 1 year, 82.4%, 71.2%, and 63.2% at 2 years, and 95.1%, 87.8%, and 85.4% at 5 years for modules 1, 2, and 3, respectively. There were no significant adverse reactions.

Conclusion: The REALITY study has demonstrated long-term effectiveness of omalizumab therapy in individuals with allergic asthma in real-life settings. The SMART tool is promising as a potential standard assessment tool to measure and define response to asthma therapy.

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Introduction

Asthma is a heterogeneous inflammatory disease that affects more than 300 million people.^{1,2} Patients with inadequately controlled asthma are at a particularly higher risk of asthma exacerbations, emergency department (ED) visits, hospitalization, and associated higher morbidity and mortality.^{1–3}

Omalizumab (Xolair; Genentech, San Francisco, California) was approved in the United States in 2003 for inadequately controlled moderate to severe allergic asthma and sensitivity to a perennial aeroallergen in patients 12 years and older and subsequently in 2016 in children aged 6 to 11 years.⁴ Most clinical trials and real-life

studies have confirmed the effectiveness, tolerability, and safety of omalizumab therapy in patients with moderate to severe allergic asthma.^{5–13} In earlier clinical trials, the primary outcome measure of response has been asthma exacerbations comparing omalizumab to placebo.^{5–7,9–11} These clinical trials also used secondary outcome measures for asthma symptoms and control, including ED department visits and hospitalizations.^{5–11} However, these trials have limitations to real-life cases given the controlled nature of prospective studies, selective enrollment criteria, and their relative short period of therapy.^{5–7,9,14} Therefore, patients participating in these clinical trials represent a small proportion of the population of patients with asthma being treated by practitioners in general practice.¹⁵ Real-life studies, however, have mainly used Global Evaluation of Treatment Effectiveness (GETE)¹⁶ to measure response.^{6,8,9,13} Most clinical trials and real-life studies have selected a 16-week omalizumab exposure period to measure treatment effectiveness and subsequently to assess response to omalizumab. Recently, few clinical trials have also included the measurements of biomarkers, such as fractional exhaled nitric oxide (FeNO), peripheral blood eosinophils, and serum periostin, to identify markers of response.^{17–19} Previous clinical trials also concur that it is difficult to predict which patients will derive a more favorable benefit from omalizumab based on their pretreatment profile.^{20–22}

Attempts have also been made to define response to omalizumab in terms of asthma control measures²³ and asthma severity.²⁴ The Asthma Control Composite defines control by mapping patient's diary-based data to parameters of asthma control.²³ The Composite Asthma Severity Index is a validated tool for determining asthma severity that can identify patients who are more likely to show a favorable response to omalizumab.²⁴ However, currently, there are no universally accepted criteria to measure response and to identify patients who may achieve better benefits from omalizumab based on their pretreatment characteristics. Despite its proven efficacy, the long-term effect of omalizumab in moderate to severe allergic asthma in real-life settings is limited. For these reasons, a standardized and validated tool for the comprehensive measurement of response to asthma therapy in real life is needed.

The Real-life Effectiveness of Omalizumab Therapy (REALITY) study was designed to evaluate the response of long-term therapy with omalizumab in patients with moderate to severe allergic asthma and to identify potential pretreatment clinical markers associated with response in a real-life clinical setting. The study had 2 aims: (1) to develop a novel response assessment tool to objectively define a positive response to long-term omalizumab therapy in real-life and (2) to identify whether any of the pretreatment clinical characteristics may be predictive of a better response to omalizumab in real life.

In this article, we focus on achieving the first aim. To better define response in real life, we developed a novel multimodular assessment tool, the Standardized Measure to Assess Response to Therapy (SMART) tool, that combines subjective assessments by treating physicians and objective measures of pertinent clinical parameters. We describe the design of the SMART tool and delineate how it can be used to measure response.

Methods

The REALITY study is a single-center, retrospectively designed, longitudinal, long-term, real-life clinical study. Study protocol was approved by the institutional review board at the University of Texas Health at San Antonio. A telephone survey was also approved and used for the study. All data files were encrypted and maintained at the Allergy and Asthma Research Center (AARC), San Antonio, Texas. The REALITY study used the SMART tool to evaluate,

compare, and investigate patient clinical characteristics before and after omalizumab therapy to identify and define responders v. nonresponders in a real-life setting.

Patient Population

Data were collected from 240 patients with uncontrolled allergic asthma who received omalizumab based on a physician's assessment of need at AARC between 2004 and 2011. The AARC is large referral clinic that specializes in allergy, asthma, and advanced therapies. To be included in study, patients required a minimum of 3 months of omalizumab treatment at AARC.

Data Collection and Variables

Patient records were reviewed retrospectively for a 12-month pretherapy period before the first dose of omalizumab. The following variables were collected at baseline and after omalizumab therapy: demographics, tobacco exposure, baseline serum IgE level, allergy testing profile, peripheral blood eosinophil counts, FeNO, asthma medications, respiratory infections, and use of antibiotics. Asthma-specific outcome variables included number of exacerbations, systemic corticosteroid use, frequency of ED visits and hospitalizations because of asthma, spirometry, and Asthma Control Test (ACT) score. An asthma exacerbation is an acute episode of progressive worsening of symptoms of asthma and generally requires a steroid treatment for a minimum of 3 days (a steroid burst). Omalizumab administered dose was recorded for each visit.

Omalizumab Dosage Regimens

Omalizumab dose and dosing frequency were determined by baseline total serum IgE level and body weight measured before the start of treatment. Omalizumab was administered by subcutaneous injections at a dose determined from the prescribing dosing table.⁴ For patients with parameters beyond the dosing table, omalizumab dosage was calculated using the standard formula to administer at least 0.016 mg/kg/IU (IgE/mL) every 4 weeks to a maximum dose of 600 mg every 2 weeks.

Assessment Time Points

After therapy initiation, patients were evaluated every 13 weeks for the first 12 months, then every 6 months for the second year, followed by yearly assessments beyond 2 years. An additional evaluation was performed at 16 weeks of treatment.

Study Visit Adherence

Visit adherence to therapy was assessed by comparing the number of omalizumab injection visits with the number of scheduled visits. Therapy adherence was calculated for all patients as the number of patients continuing therapy at any desired period compared with all patients who initiated omalizumab therapy.

Assessment of Response to Therapy

The SMART tool is a 3-module approach to assess the response to therapy (Table 1). Module 1 (M1) used the subjective assessment by GETE by the health care professional based on patient encounters. Module 2 (M2) included an objective evaluation of 6 pre-identified clinical parameters before and after therapy. Module 3 (M3) combines both M1 and M2. Response to omalizumab for each patient was evaluated using the SMART tool by M1, M2 and M3 independently at the desired assessment periods (eAppendix 1).

For M1, GETE was assessed by physician on a 5-point score-card as follows: 4, complete control; 3, marked improvement in control; 2, limited control; 1, no change in control; and 0, worsening of control. M1 defines responders as patients with improvement or complete control, whereas patients with limited or no

improvement or worsening of control were classified as non-responders. GETE was completed retrospectively by physician investigators as part of the study and not as standard of practice.

M2 evaluates 6 objective parameters of asthma control and burden independently at any therapy time point compared with the preomalizumab period. Reduction rates of 50% or higher were found for (1) asthma exacerbations, (2) steroid treatment, (3) emergency or unscheduled health care visits, (4) hospitalizations, (5) improvement in mean forced expiratory volume in 1 second (FEV₁) ($\geq 12\%$ and 200 L), and (6) improvement of ACT score mean (≥ 3 points). All 6 parameters were weighted equally and were scored separately giving a point score of 0 (not met) or 1 (met). Patients with total M2 scores of 3 or higher of 6 positive response parameters were defined as responders, whereas patients with a score of less than 3 were considered nonresponders.

M3 combines assessment of response by M1 and M2 to define true responders as patients who were considered responsive by both M1 and M2 and not true responders if either one or both M1 and M2 criteria were not met.

Statistical Analysis

Study data were analyzed by Research Statistical Consultant Inc. Responders were identified for M1, M2, and M3 independently at all timelines. We conducted χ^2 *t* tests to analyze the statistical significance differences among various parameters for responders vs non-responders. Descriptive analyses were performed for sex, age, serum IgE level, omalizumab dosage, adherence, allergic score, and eosinophil count with response modules M1, M2, and M3 independently.

Results

Demographics

Data from 240 patients were evaluated, and the data of 198 patients (100 males and 98 females) were included in the analysis (Table 2). Forty-two patients were excluded from evaluation because of receiving omalizumab therapy for less than 3 months, nonadherence, or insufficient medical records of asthma-related events for the 12 months before therapy initiation. At therapy initiation, 111 patients (56.1%) were adults 18 years or older (range, 18–77 years), 47 (23.7%) were children younger than 12 years (range, 3–11 years), and 40 (20.2%) were adolescents of 12 to younger than 18 years. Of these, 93 (46.9%), 63 (31.8%) and 38 (19.2%) were Hispanic, white, and African American, respectively. The mean age at first omalizumab injection was 31.6 years (range, 3–77 years).

Omalizumab Dosage

The mean omalizumab dose received by the 198 patients was 473 mg every 4 weeks (range, 66–1200 mg) (Table 2). Dosage

received was also calculated for baseline IgE levels and weight. Total doses received were 1.336 mg/IgE every 4 weeks (range, 0.059–9.108 mg/IgE every 4 weeks) and 0.0181 mg/IgE/kg every 4 weeks (range, 0.0006–0.1191 mg/IgE/kg every 4 weeks) (Fig 1). Mean therapy duration was 2.49 years (range, 3 months to 8 years). During therapy, 198 patients received a mean total of 13,441 mg (range, 600–57,525 mg).

Study Visit Adherence

A total of 10,128 injection visits were scheduled for 198 patients as calculated by the recommended regimen. The number of total injection administration visits was 7890. Overall clinic visit adherence was 78% (Table 2). More than 16,000 injections were administered to 198 patients between 2004 and 2011 at the AARC. No serious adverse events, including anaphylaxis, were reported.

Therapy Adherence

Adherence to omalizumab therapy was calculated at different periods (Table 2). Patients had therapy adherence rates of 98.0%, 79.8%, 63.1%, 43.9%, 27.8%, and 20.7% at 16 weeks, 1 year, 2 years, 3 years, 4 years, and 5 years, respectively (Fig 2).

Omalizumab Response by the SMART Tool (a Multimodular Assessment)

Response rates were assessed independently by all 3 modules (M1, M2, and M3) of the SMART tool at all periods (Table 3). The total number of patients decreased over time to 158, 125, and 41 at 1 year, 2 years, and 5 years. The number of responders and the response rates as assessed at 16 weeks and years 1, 2, and 5 were 119 (61.3%), 134 (84.8%), 103 (82.4%), and 39 (95.1%), respectively, in M1 and 118 (60.8%), 114 (72.2%), 89 (71.2%), and 36 (87.8%), respectively, in M2. However, these numbers were 81 (41.8%), 102 (64.6%), 79 (63.2%), and 35 (85.4%), respectively, in M3 (Fig 3). The sample size beyond 5 years was too low to have significance.

Baseline IgE Levels

Baseline IgE levels were measured for all patients before therapy initiation. The mean baseline IgE level was 1046 IU/mL (range, 23–10,979 IU/mL), whereas the median level was 433 IU/mL (Table 2).

Discussion

The REALITY study is one of the largest retrospective observational studies evaluating the long-term response to omalizumab therapy in patients with uncontrolled moderate to severe allergic asthma in a real-life clinical setting. By using the SMART tool, it was possible to compare the patient's clinical characteristics before and after treatment and assess response.

Table 1

Standardized Measure to Assess Response to Therapy (SMART)

1. Module 1 (M1): Responders identified by physicians (GETE) only:				
• Responders (RM1): patients with complete control or marked improvement • Nonresponders (NRM1): patients with limited or no improvement or worsening of control				
2. Module 2 (M2): Responders identified by 6 clinical parameters				
a. $\geq 50\%$ reduction in number of asthma exacerbations (annualized) b. $\geq 50\%$ reduction in number of systemic steroid treatment (oral, intravenous, or intramuscular) (annualized) c. $\geq 50\%$ reduction in number of emergency or unscheduled health care visits (annualized) d. $\geq 50\%$ reduction in number of hospitalizations for asthma (annualized) e. Improvement in mean FEV₁ ($\geq 12\%$ and ≥ 200 mL) f. Improvement in mean ACT score (≥ 3 points)				
• Responders (RM2): patients with ≥ 3 of 6 positive response parameters • Nonresponders (NRM2): patients with < 3 of 6 positive response parameters				
3. Module 3 (M3): Responders by both M1 and M2				
TRUE RESPONDER (RM3)	=	RESPONDER by MODULE 1 (RM1)	+	RESPONDER by MODULE 2 (RM2)

Abbreviations: ACT, Asthma Control Test; FEV₁, forced expiratory volume in 1 second; GETE, Global Evaluation of Treatment Effectiveness; NRM1, nonresponder by M1; NRM2, nonresponder by M2; RM1, responder by M1; RM2, responder by M2; RM3, responder by M3 (true responder).

Table 2
Demographics and Characteristics of the REALITY Study Patients

Characteristic	Finding (N = 198) ^a
Sex	
Male	100 (51)
Female	98 (49)
Age at therapy initiation, y	
Mean (SD)	31.7 (20.9)
Median (range)	30.5 (3–77)
Children (<12 y)	47 (23.7)
Adolescents (12–<18 y)	40 (20.2)
Adults (≥18 y)	111 (56.1)
Ethnicity	
Hispanic	93 (46.9)
White	63 (31.8)
African American	38 (19.2)
Others	4 (2.1)
Omalizumab dosage received, mean (range)	
Total dose, mg per 4 wk	473 (66–1200)
Total dose, mg/IgE per 4 wk	1.336 (0.059–9.108)
Total dose, mg/kg/IgE per 4 wk	0.0181 (0.0006–0.1191)
Total omalizumab per patient (cumulative), mg	13,441 (600–57,525)
Visit adherence for all patients, %	78
Baseline IgE, IU/mL	
Mean	1046
Median	433
30–700 IU/mL	131 (66.2)
Level >700 IU/mL	67 (33.8)
Allergy profile score, mean (SD)	
Perennial (4 allergens)	1.97 (1.11)
Seasonal (4 allergens)	2.39 (1.42)
Total (combined 8 allergens)	4.36 (2.11)

Abbreviations: REALITY, Real-life Effectiveness of Omalizumab Therapy.

^aData are presented as number (percentage) of patients unless otherwise indicated.

On the basis of the importance and unmet need for a more accurate and comprehensive measure of response, we developed a composite response assessment tool, the SMART tool, which is a 3-module approach that can assess the response to therapy at any desired time point. It combines the subjective assessment by health care professionals based on patient encounters (M1), an objective evaluation of 6 clinical parameters of asthma control (M2), and a combination of both (M3) to identify patients who are true responders.

In the REALITY study, the responder rates varied based on the assessment modules. This finding highlights the differences that may exist between objective and subjective evaluations in asthma and response to therapy. M3 identified fewer responders because it was more rigorous by design, combining both types of assessments. In addition, only a small number of patients were considered responsive to only one module (M1 or M2). Although there is no

consensus on the exact definition of a responder to biological therapies in asthma,^{12–15,19–21} using both objective and subjective findings likely yield the best approximation of a true responder (M3). Of our patients, 42% and 65% were considered true responders by M3 at 16 weeks and 1 year, respectively. This finding is comparable to the overall response rate to omalizumab globally.^{13,15,16,19–21} The fact that response was well maintained beyond 1 year provides further evidence of the persistency of long-term response to omalizumab therapy.^{20,21} These results are comparable to most of clinical trials in real-life worldwide.^{20,21,25–27} All 3 modules showed an increase in response rates over time. The higher response-rate of 85% (by M3) at the 5-year period corresponds to the comparatively lower sample size but is also influenced by the treating physician's decision to continue prescribing the medication beyond 12 months in patients with a favorable response.

The SMART tool has several important characteristics. This tool uses a more comprehensive evaluation in clinical settings comparing patients to themselves ($n = 1$) before and after initiation of therapy. More importantly, response can be assessed at any desired time point to identify when a patient first responds and may be used to determine maintenance of response. To date, because there are no unified criteria available to assess the response to asthma therapy worldwide,^{20,21} it is difficult to monitor the therapy effectiveness.^{23,24} The SMART tool provides a novel method to identify responders and nonresponders in real-life clinical setting. A positive response by M1 measured subjectively by GETE as patients showing complete or markedly improved control compared with baseline and a positive response by M2 for objective clinical parameters as defined by 50% or more improvement from pretreatment baseline for asthma exacerbations, steroid treatment, emergency or unscheduled health care visits, and hospitalizations were independently significant. However, improvement in FEV₁ ($\geq 12\%$ and ≥ 200 mL) and ACT score (≥ 3) are validated measures for minimal improvement difference for asthma control^{28–30} to be clinically meaningful and therefore are significant as response measures. A positive response for M3 was assessed as patients who had positive responses by both M1 and M2 modules. Moreover, response was measured for each patient independently comparing all parameters to baseline for themselves only ($n = 1$) and labeled as responder or nonresponder. Thus, any patient identified as a responder using a 3-module assessment corresponds to a significant response to therapy.

Patients required a minimum of 3 months of exposure to omalizumab to be included in this study. This amount was based on the mechanism of action of omalizumab and time needed to down-regulate high-affinity IgE receptor expression on mast cells and basophils.^{31,32} In our study, patient therapy duration varied widely

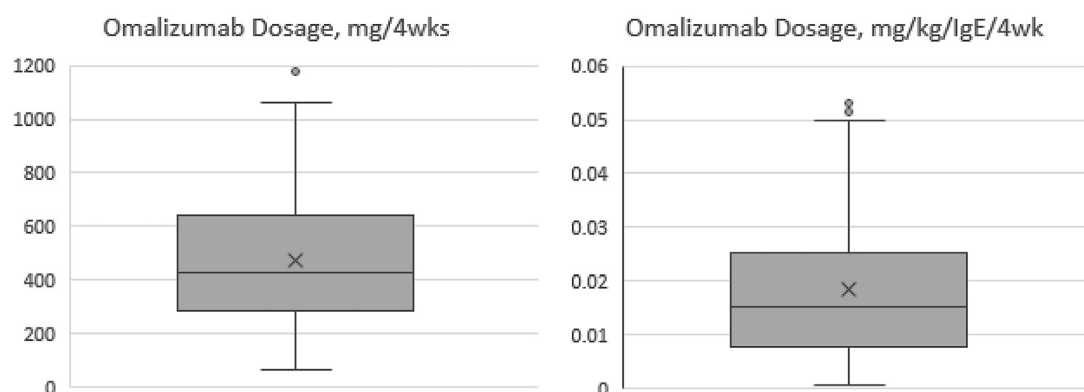


Figure 1. Mean omalizumab dosage received.

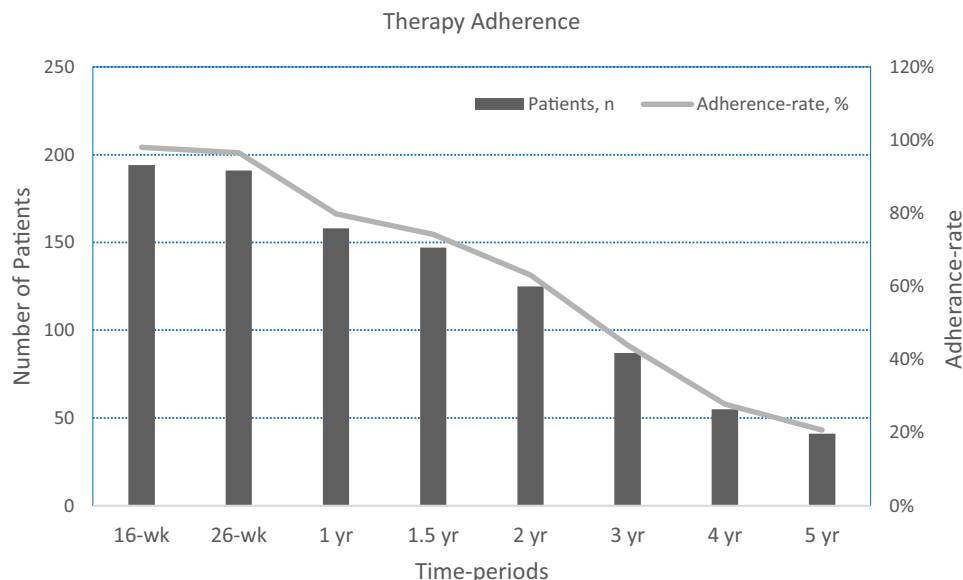


Figure 2. Adherence to omalizumab therapy during a 5-year period.

from 3 months to 8 years. Each patient was individually evaluated and assessed for response compared with herself/himself ($n = 1$) from the pretreatment period. Overall responses for all patients were also evaluated at all time points. Quarterly assessments enabled us to identify patients as responders vs nonresponders and thus identify the time point of the first positive response. This enables one to assess the response pattern and follow persistency of response of ongoing therapy.

During therapy, the mean omalizumab dose received by 198 patients was 473 mg every 4 weeks (range, 66–1200 mg every 4 weeks), and patients received a mean total of 13,441 mg (range, 600–57,525 mg) during therapy. Patients received a mean of 0.0181 mg/IgE/kg every 4 weeks, which is within 12% of the recommended omalizumab dosage using the standard formula to administer at least 0.016 mg/kg/IU (IgE/mL) during every 4-week period range.⁴ However, given the wide dosage range for all patients, there would be at least 2 extreme subgroups of patients: those who were undertreated and those who were overtreated with omalizumab. To date, limitations remain on assessing the response to omalizumab and hence to assess the need of any dosage and/or frequency adjustments and deciding to continue or discontinue omalizumab therapy.^{27,33} Because of the lack of recommendations on omalizumab dosage and/or frequency changes after therapy initiation⁴ and contrary to fixed dosage regimens in omalizumab controlled trials,^{6,7,9,14,18,19} monitoring the individualized pattern and level of response at any desired time point, the SMART tool may provide further therapeutic guidance.

Response rates by M1 were higher than M2 at every time point. Thus, by SMART tool module design, M2 is the limiting factor for the corresponding lower response by M3 at that time point. It directly infers that the health care practitioners are more likely to subjectively assess patients as responders compared with the objective assessment of clinical parameters of asthma control. Even though GETE (M1) is important,¹⁶ it may be highly variable from practice to practice and from country to country. Thus, we should not rely solely on the GETE to assess response. Objective measures (M2) should be more optimized toward a universal composite assessment tool of measuring response to therapy. Because the SMART tool combines subjective and objective assessments, it thus provides a more comprehensive assessment.

Adherence and Safety

The overall adherence rate for omalizumab administration was 78% for the AARC. As with the other real-life studies,²⁷ our data also indicate a comparatively higher earlier adherence rate that decreased over time.^{27,34} Patient adherence to omalizumab therapy decreased consistently by 20% (range, 17%–23%) annually, which is comparable to the reported overall global annual adherence rate for omalizumab.³⁵ Patients were dropped from treatment because of various nonadherence reasons, patient decision regarding lack of efficacy, and insurance issues.

With more than 16,000 injections administered to 198 patients during an 8-year period, no serious adverse events, including anaphylaxis, were reported. Thus, our results further support the safety profile of omalizumab.^{5–9}

Strengths and Limitations

There are a few limitations in our study that deserve mention. First, the study has the inherent limitations of a retrospective design and thus is limited based on available data. Because this was a retrospective data abstraction, there were no specific criteria for exacerbations that do not require steroid bursts. As a standard of clinical practice, a minimum 3 days of steroid treatment made it a burst. In addition, for 2 consecutive steroid bursts given within 7 days, it was solely at the physician's discretion to decide if it was a prolonged exacerbation or 2 separate exacerbations. It was not plausible to separate these exacerbations retrospectively. Second, the study was performed in a single center; hence, our findings should be extended to other patient populations with caution.

Table 3
Responders by 3 Modules (M1, M2, M3) of SMART

Module	No. (%) of responders				
	13 Weeks	16 Weeks	1 Year	2 Years	5 Years
M1	114 (57.6)	119 (61.3)	134 (84.8)	103 (82.4)	39 (95.1)
M2	110 (55.6)	118 (60.8)	114 (72.2)	89 (71.2)	36 (87.8)
M3	76 (38.4)	81 (41.8)	102 (64.6)	79 (63.2)	35 (85.4)
Total patients	198	194	158	125	41

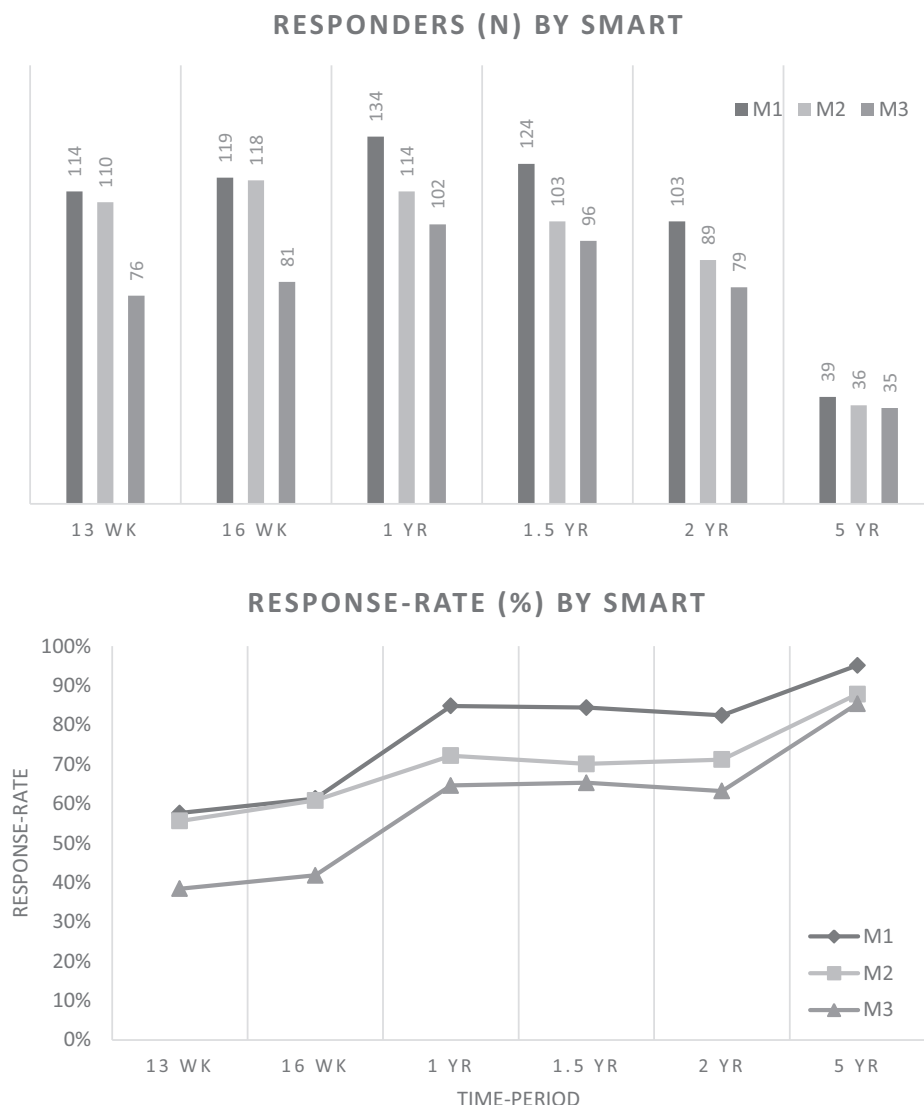


Figure 3. Responders and response rate by Standardized Measure to Assess Response to Therapy (SMART) (modules 1, 2, and 3).

Third, the SMART tool has not been validated as an assessment tool for asthma and some overlap exists in terms of assessment characteristics of asthma exacerbation and control among M1 and M2. Nevertheless, there is no gold standard for the assessment of response to omalizumab or other biologicals in asthma.^{5-10,12,13,15} By using variables that are clinically relevant and used in clinical trials, the SMART tool is able to provide an approximation response and may facilitate decisions regarding continuation of therapy. Fourth, the overall response rates were assessed for all patients continuing therapy at the assessment points and thus are potentially biased especially at later time points because the patients who benefit from the treatment tend to stay on it and non-responders may discontinue treatment over time. However, the reassuring fact is that patients who respond to the drug and continue to take the drug in the long term will more likely maintain response. On the contrary, no data on response are available for patients who discontinued omalizumab treatment. Fifth, the SMART tool was used in patients treated with omalizumab and may not necessarily be applicable to the assessment of response to other therapies. Despite these limitations, the REALITY study is one of the largest retrospective, observational studies to evaluate the long-term response to omalizumab therapy in a real-life clinical setting. In addition, patients assessed in most clinical trials based

on selective criteria^{6,9,14,18} do not necessarily reflect the real-world experience.¹⁹ Thus, compared with prospective trials, the results of the REALITY study may be more closely applicable to real-life clinical settings.

Clinical Significance and Conclusions

The REALITY study has confirmed long-term effectiveness of omalizumab therapy in patients with allergic asthma in real life. The SMART tool presents promise as a potential assessment tool to measure and define response to asthma therapy. Response rates by subjective assessment of the physician (M1) is often higher than the objective assessment of parameters of asthma control (M2), highlighting the need for a more objective response assessment tool. The combined assessment module (M3) provides a more accurate measure of response to omalizumab in real life. Furthermore, the SMART tool may provide guidance necessary to make decisions and changes in omalizumab and other asthma therapies.

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References

- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2018. <http://www.ginasthma.org/>. Accessed May 31, 2019.
- American Academy of Allergy, Asthma and Immunology. Asthma Statistics. 2019. <http://www.aaaai.org>. Accessed May 31, 2019.
- Center for Disease Control and Prevention. CDC's National Asthma Control Program Grantees. Atlanta, GA: US Dept of Health and Human Services, Centers for Disease Control and Prevention; 2013.
- Omalizumab (Xolair) [full prescribing information]. https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed May 31, 2019.
- Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy*. 2005;60(3):302–308.
- Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med*. 2011;364:1005–1015.
- Brusselle G, Michils A, Louis R, et al. "Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: the PERSIST study. *Respir Med*. 2009;103(11):1633–1642.
- Holgate S, Buhl R, Bousquet J, Smith N, Panahloo Z, Jimenez P. The use of omalizumab in the treatment of severe allergic asthma: a clinical experience update. *Respir Med*. 2009;103(8):1098–1113.
- Hanania NA, Alban O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154(9):573–582.
- Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol*. 2009;124:1210e6.
- Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18:254e61.
- Chippes BE, Lanier B, Milgrom H, et al. Omalizumab in children with uncontrolled allergic asthma: review of clinical trial and real-world experience. *J Allergy Clin Immunol*. 2017;139:1431–1444.
- Braunstaal GJ, Chen CW, Maykut R, Georgiou P, Peachey G, Bruce J. The eXpReience registry: the 'real-world' effectiveness of omalizumab in allergic asthma. *Respir Med*. 2013;107:1141–1151.
- Nowak D. Management of asthma with anti-immunoglobulin E: a review of clinical trials of omalizumab. *Respir Med*. 2006;100(11):1907–1917.
- Casale TB, Chippes BE, Rosén K, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy*. 2018;73(2):490–497.
- Bousquet J, Rao S, Manga V. Global evaluation of treatment effectiveness (GETE) is an accurate predictor of response to omalizumab in patients with severe allergic asthma: a pooled analysis. *Eur Respir J*. 2014;44:P3483.
- Holgate S, Smith N, Massanari M, Jimenez P. Effects of omalizumab on markers of inflammation in patients with allergic asthma. *Allergy*. 2009;64(12):1728–1736.
- Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187(8):804–811.
- 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 [published online May 22, 2018]. *J Allergy Clin Immunol Pract* <https://doi.org/10.1016/j.jaip.2018.04.043>.
- Bousquet J, Rabe K, Humbert M, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. *Respir Med*. 2007;101(7):1483–1492.
- Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest*. 2004;125(4):1378–1386.
- Bhutani M, Yang WH, Hébert J, de Takacs F, Stril JL. The real world effect of omalizumab add on therapy for patients with moderate to severe allergic asthma: the ASTERIX observational study. *PLoS One*. 2017;12(8):e0183869.
- Harris JM, Wong DA, Kapp AV. Development of the Asthma Control Composite outcome measure to predict omalizumab response. *Ann Allergy Asthma Immunol*. 2011;107:273–280.
- Wildfire JJ, Gergen PJ, Sorkness CA, et al. Development and validation of the Composite Asthma Severity Index—an outcome measure for use in children and adolescents. *J Allergy Clin Immunol*. 2012;129:694–701.
- Bousquet J, Siergiejko Z, Swiebocka E, et al. Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. *Allergy*. 2011;66(5):671–678.
- Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol*. 2017;140(1):162–169.
- Nurkić J, Al-Ahmad M, Maher A, et al. Most common, real life factors affecting effectiveness of omalizumab asthma treatment: a 10-year study. *Med Glas (Zenica)*. 2019;16(1):45–52.
- Donohue JF. Minimal clinically important differences in COPD lung function. *COPD*. 2005;2:111–124.
- Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J*. 1999;14:23–27.
- Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol*. 2009;124:719–723.e1.
- Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεRI expression and function. *J Allergy Clin Immunol*. 2004;114(3):527–530.
- MacGlashan Jr DW, Bochner BS, Adelman DC, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol*. 1997;158(3):1438–1445.
- 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.
- Singh H, Peters J, Kaur Y, Diaz J. Impact of visit compliance on response to omalizumab therapy in a real-life clinical setting: reality study. *J Allergy Clin Immunol*. 2016;137:AB13.
- 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(1):128.

eAppendix 1. Supplemental Information

1. FEV₁ improvement criteria with 12% and 200 mL

We would like to clarify that these forced expiratory volume in 1 second (FEV₁) improvement criteria are not additive. For FEV₁ improvement, the patient should have an increase of 12% and at least 200 mL compared with baseline. This is in agreement with American Thoracic Society definition of significant reversibility and is consistent with most clinical trials.

2. Asthma exacerbation and steroid burst

An asthma exacerbation is an acute episode of progressive worsening of symptoms of asthma and generally requires a steroid treatment for minimum of 3 days (a steroid burst). Because this was retrospective data abstraction, there were no specific criteria for exacerbations that do not require steroid burst. As standard of clinical practice, a minimum of 3 days taking steroids made it a burst. In addition, for 2 consecutive steroid bursts given within 7 days, it was solely at the physician's discretion to call it a prolonged exacerbation or consider these as 2 separate exacerbations. It was not plausible to separate these exacerbations retrospectively.

3. Scoring M2 parameters in different scenarios

Parameters a to d of module 2 (M2) are related to asthma exacerbations, and there is overlap. Truly, asthma exacerbation severity scale is highly variable. It can be an exacerbation that requires just steroid burst (total score, 2; 1 each for a and b); a moderate to severe exacerbation that requires an emergency department (ED) visit (total score, 3; 1 each for a, b, and c); or a very severe exacerbation that requires hospitalization (total score, 3; 1 each for a, b, and d). Any exacerbation that had an ED visit and that ended in hospitalization would be considered hospitalization only and not for both ED and hospitalization and will not receive a total score 4 (1 each for a, b, c, and d). In those cases, an ED visit is considered transient phase only, and hence no score is given. By definition of asthma exacerbation, almost every exacerbation ends up getting a steroid burst and hence a score of 2 (1 each for a and b). Thus, by virtue of exacerbation definition and M2 design, despite being scored independently, all 4 parameters of asthma exacerbation (a, b, c, and d) are interrelated and provide corresponding weighted score based on asthma exacerbation severity.

4. Spirometry and Asthma Control Test score in younger children

In general, younger children filled out the Asthma Control Test with their parents and/or guardians. It is always challenging to have acceptable spirometry and FEV₁ in younger children. We had only one 3-year-old and a total of only 4 children who are younger than 6 years of age at the start of therapy. For these 4 patients, spirometry was not performed (recommended only for those 6 years and older). When spirometry was unable to be performed, it was excluded from data point.

5. Adherence calculation: cancelled or no-show visits

For all patients, dosage and frequency of omalizumab administration were calculated before therapy initiation. Hence, by virtue of design and to be consistent with the visit adherence formula, all cancelled and/or no-show visits are still counted in the denominator. Only actual drug administration visits will be counted as numerator for that assessment period.

6. Allergy profile scoring

For all patients, sensitivities by skin prick or radioallergosorbent test were recorded for a total of 8 allergens: 4 perennial (cat, dust mites, cockroach, mold) and 4 seasonal (tree, grass, weed, mountain cedar). For each patient, perennial and seasonal sensitivity scores were calculated separately (number of positive allergens of a possible 4). Combined sensitivity scores were also calculated for all 8 allergens.