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Acceptance and results of therapy with omalizumab in real world Kerala setting: reports from the ARTWORK study, Kerala, South India

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ABSTRACT

Objective: Despite the availability of effective medications, only a minority of asthma patients achieve guideline defined asthma control. Treatment success depends on patient concurrence to the prescribed drug and adherence to treatment. It is therefore crucial to identify the patient preferences as well as attitudes towards asthma medications. Omalizumab is recommended as a preferred option in step 5 of asthma therapy. There have been few studies to address patient perspectives on omalizumab therapy in India.

Methods: This was a retrospective study. Patients with inadequate asthma control were considered for the study. Systematic evaluation was done to identify and correct modifiable factors that can worsen asthma control. Patients with persisting poor asthma control who were deemed suitable to receive this agent were evaluated with their attitudes toward acceptance or refusal and the reasons for opting out were noted. The patients who received omalizumab were followed up to determine the results of treatment and duration of adherence to therapy.

Results: Thirty-five patients out of 51 patients chose to avoid this drug. The reasons for opting out included erroneous perception of optimal asthma control, cost of therapy, and concern about adverse effects. Patients took omalizumab for a median duration of 6 months. Improved asthma control and decreased frequency of exacerbation was noted in all patients which persisted during the 6-month follow-up.

Conclusions: The majority of patients needing step 5 therapy opt out of omalizumab. Cost of drug, duration of therapy and erroneous perception of good asthma control account for refusing treatment. Omalizumab affords excellent clinical benefits to patients who receive it, and the benefits extend beyond the duration of therapy.

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Introduction

Asthma is an exceedingly common problem met with in clinical practice. Global estimates suggest that 300 million of the world's population have asthma. A projected 37.9 million Indian citizens are asthmatic, the number equaling 55% of the UK population (1). The disease burden of asthma in India is substantial and outweighs the number of people with HIV infection or tuberculosis. The phase 3 International Study of Asthma and Allergy in Children revealed that 7% of Indian children were wheezers, with a substantially greater occurrence of up to 10–20% in certain geographic pockets (2).

The cornerstone of asthma management is trigger avoidance and topical anti-inflammatory therapy. Despite the availability of effective therapy, population-based studies conducted across multiple

continents provide information that only a small percent of asthmatics in Asia achieve guideline defined asthma control (3,4). The impact of poor asthma control is substantial, both in terms of quality of life and utilization of healthcare resources (5). This is of particular concern in Asia where uniform access to quality care is found lacking. The Asia-Pacific Asthma Insight and Management (AP-AIM) study (6) was aimed at understanding multiple aspects of asthma including level of asthma control and its impact on quality of life across eight countries including India. Four hundred asthmatics from across India were evaluated in the AP-AIM study. Ninety-one percent of the asthmatics in India believed that their asthma was under optimal control; however, none of these asthmatics met the asthma treatment goals when assessed

by objective measures. Up to 2 emergency doctor visits a year was acceptable to Indian patients and they believed that this may be labeled as optimum control. Eighty-nine percent of Indian asthmatics committed to using short courses of oral steroids 10.5 times a year. Only 36% of Indian asthmatics used controller inhalers with a majority preferring the oral route of asthma medication.

The treatment success in asthma revolves around patient beliefs, their acceptance of the prescribed medications and subsequent adherence to treatment regimens. Hence identifying the attitudinal determinants of asthma control is of paramount importance. Medications prescribed should match the patient preferences and should be affordable. An Asian study (7) identified five patient-clusters defined in terms of their asthma control and attitude toward asthma therapy. The authors have stressed that individualization of pharmacotherapy (broadly adhering to guidelines) may be needed tailoring to the needs of each cluster. There has been a paucity of data on the attitude of asthmatic patients on omalizumab therapy, but studies exploring the beliefs and practices of clinicians regarding the use of biological therapies (8) in severe asthma are available.

The end point of therapy with omalizumab is not defined. Treatment with biologics have substantial economic implications, specially so considering the fact that these agents are recommended to be continued for years when efficacious. Hence, studies addressing whether they can be safely withdrawn after a short course of treatment or need to be continued for a longer course of years may be beneficial (9). However, evidences that can guide clinicians with such decisions are sparingly available. A prospective study evaluated the asthma control in patients adhering or opting out from long-term omalizumab treatment (10). However, such studies from India are not available. The duration for which Indian patients adhere to omalizumab therapy is largely unknown. The present study attempts to explore the real world acceptance and benefits of omalizumab in Indian patients.

Objectives

The present study was undertaken with the following objectives:

1. The acceptance rate of omalizumab therapy in patients with severe asthma needing step 5 of therapy as per GINA guidelines
2. The reasons for denying treatment with omalizumab in those patients who opted out

3. Assessment of asthma control in patients treated with omalizumab during the duration of therapy
4. The duration for which omalizumab therapy was administered to the patients
5. Assessing the level of asthma control (with asthma control test) at 6 months after discontinuing omalizumab

Materials and methods

The present study was a retrospective study based on review of hospital records. The study patients have been managed at an out-patient setting.

Selection of study participants

The pulmonary medicine department of the institution runs a severe asthma clinic and maintains EMR data of all outpatients including severe asthmatic patients. Patients attending the pulmonary medicine department of Rajagiri hospital between January 2017 and December 2019 with partly controlled or uncontrolled asthma (based on the GINA guidelines) were considered for the study. Noncompliance to therapy, incorrect inhaler technique, persistent triggers and comorbidities worsening asthma control were identified. Non compliance to therapy was enquired and daily inhaler compliance was ensured based on dose meter count at the subsequent visit. Inhaler technique was supervised and corrected. Gastroesophageal reflux evaluation with laryngoscopy and thyroid function tests were done and abnormalities were corrected. We reserve omalizumab therapy to asthmatic patients who remain uncontrolled despite step 4 therapy (as per GINA guidelines). Patients with persisting poor asthma control despite corrective steps underwent evaluation as per the asthma treatment protocol of the hospital for suitability with omalizumab therapy based on body weight, IgE level and allergen sensitivity testing. All patients who were potential candidates for omalizumab treatment were identified from hospital records and were included in the study.

Exclusion criteria

The following patients were excluded from the study:

1. Age less than 12 years
2. Pregnant or lactating ladies
3. Patients with active malignancy or HIV disease

4. Patients who are on any other monoclonal antibody therapy or have received such agents in the last 1 year

Sample size

In the absence of previous similar studies from India and considering the small number of patients available, all uncontrolled asthmatic patients who were suitable for therapy with omalizumab were analyzed.

Study methods and data entry

Omalizumab therapy was offered to suitable patients and acceptance of therapy was left to the patient based on an informed shared decision making. In those patients who preferred against omalizumab usage, the reason for opting out was noted. The drug was administered to patients who consented to omalizumab therapy in recommended doses based on body weight and pretreatment serum IgE levels. The duration of therapy was noted down from EMR. The response to therapy was noted with regard to asthma control (measured with the asthma control test [ACT]), ability to step down medications, exacerbation rate etc. Patients were followed up after discontinuation of omalizumab therapy and asthma control at 6 months after discontinuation of the drug was assessed.

Frequency of exacerbations was measured as the annual rate of exacerbations. The baseline frequency of exacerbations was defined as the number of exacerbations in the 6 months prior to administering the first dose of omalizumab multiplied by 2 (multiplied by 12 and divided by 6). Exacerbation at 6 month was the number of exacerbations in the 6 months after administering the first dose of omalizumab multiplied by 2. Exacerbation at 6 months of stoppage of therapy was the number of exacerbations in the 6 months after administering the last dose of omalizumab multiplied by 2. Mean daily steroid use was defined as the daily steroid use in the month prior to initiation of omalizumab, sixth month of omalizumab use and sixth month after stopping omalizumab. The total oral steroid consumption (in mg/day of prednisolone or equivalent) was divided by the number of days in the month to calculate the average daily dose.

Data were tabulated in Microsoft spreadsheet and simple descriptive data on rate of omalizumab acceptance, reason for opting out and duration of therapy is being presented.

Statistical analysis

Data analysis was done using IBM SPSS software version 26.0. Categorical variables were presented as number and percentage. Qualitative variables were expressed as mean $\pm$ SD. For the description of the continuous variables, methods of descriptive statistics with calculation of average and standard deviation were used. The paired *t*-test or dependent sample *t*-test was used for a comparison of continuous variables. The chi-square test was used to compare categorical variables. The level of statistical significance was considered to be $p < 0.05$. The data were compared for the observations made at baseline, at 6 months after initiation of treatment and 6 months after cessation of the treatment (or 12 months from baseline). The effect of omalizumab on asthma control (assessed by the ACT), frequency of exacerbations and mean daily use of oral steroids was evaluated.

Ethical committee approval

Approval to conduct the study was obtained from the hospital ethical committee. (Ethics committee letter number RHEC – No. RAJH 2020/010). Anonymity of study participants was ensured. Considering the retrospective nature of the study, need for informed patient consent was waived off by the ethical committee.

Results

We had a total of 560 patients with uncontrolled asthma encountered during the study period. However, on systematic evaluation, most of them had non compliance to inhaled medications, poor inhaler technique, recurrent exposure to triggering factors etc as the cause for lack of asthma control. After correction of these modifiable factors, 51 patients had persisting poorly controlled asthma as per the GINA guidelines. The low numbers of patient who qualify for step 5 treatment may be a testimony to the fact that most patients with uncontrolled asthma have simple modifiable factors as opposed to need for high end treatment like biologicals.

Baseline characteristics

There were a total of 51 patients with uncontrolled asthma who were analyzed based on the hospital records. The mean age of study subjects was 44.2 years and 28 patients were males. Thirty-four out of 51

patients had educational qualification of degree level or beyond. The mean duration asthma was 8.2 years. These data are shown in Table 1.

Acceptance rate of omalizumab and reasons for rejection

51 patients were found suitable for therapy. Of these, omalizumab was administered in 16 patients after discussion on the expected efficacy, adverse events, cost of therapy and duration. Thirty-five patients opted out of omalizumab therapy. Of these, 16 patients erroneously felt that their asthma control was optimal. Eleven patients were concerned about the cost of therapy. Five patients did not prefer an injectable drug for asthma. Three patients were concerned about the fact that the duration of therapy was not well defined. The reasons for denying omalizumab therapy are depicted in Figure 1.

Table 1. Baseline characteristics of study population.

Parameter	Number of patients
Age	
Less than 20 years	4
20–50 years	27
More than 50 years	20
Gender	
Male	28
Female	23
Educational status	
Less than 10th standard pass	2
10th to 12th standard	15
Degree or above	34
Duration of asthma	
Less than 5 years	8
5–10 years	36
More than 10 years	7

Real world improvement in asthma during and after omalizumab treatment

Asthma control (measured by the ACT), number of exacerbations and maintenance dose of systemic steroids (measured as the mean daily steroid dose in mg/day of prednisolone or equivalent) use at baseline, 6 months of omalizumab therapy and 6 months after stopping omalizumab are summarized in Tables 2 and 3 as well as Figure 2.

The ACT results indicate significant improvement in asthma control with 6 months of treatment with omalizumab which was sustained even 6 months after

Table 2. Clinical efficacy of omalizumab.

Parameter	N	Therapy	Mean $\pm$ SD
Asthma control test	16	Baseline	14.56 $\pm$ 2.00
		Month 6	18.81 $\pm$ 2.26
		Month 12	19.06 $\pm$ 1.73
Mean exacerbations	16	Baseline	2.44 $\pm$ 0.89
		Month 6	0.56 $\pm$ 0.73
		Month 12	0.50 $\pm$ 0.63
Oral steroid use	16	Baseline	3.25 $\pm$ 1.34
		Month 6	1.19 $\pm$ 0.75
		Month 12	0.88 $\pm$ 0.72

Table 3. Comparison of efficacy at 6 and 12 months versus baseline.

Parameter	Comparison	95% CI	P-value
Asthma control test	Baseline vs month 6	−5.74 to −2.76	<0.0001
	Baseline vs month 12	−5.55 to −3.45	<0.0001
	Month 6 vs month 12	−1.66 to 1.16	0.7108
Mean exacerbations	Baseline vs month 6	1.40 to 2.35	<0.0001
	Baseline vs month 12	1.63 to 2.24	<0.0001
	Month 6 vs month 12	−0.43 to 0.56	0.7915
Oral steroid use	Baseline vs month 6	1.27 to 2.85	<0.0001
	Baseline vs month 12	1.60 to 3.15	<0.0001
	Month 6 vs month 12	−0.26 to 0.89	0.2644

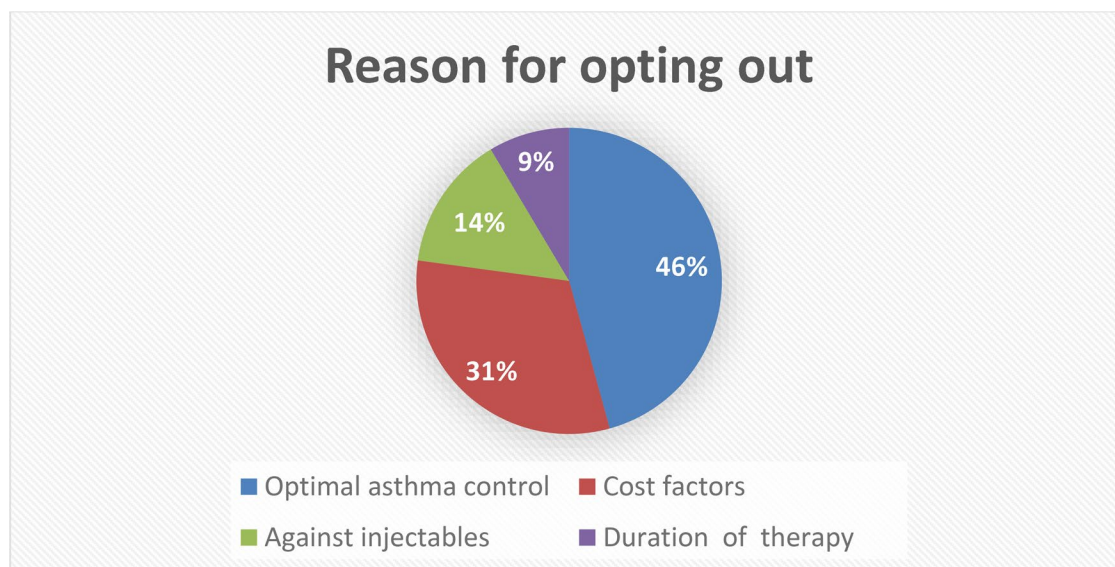


Figure 1. Reasons for preferring against omalizumab therapy.

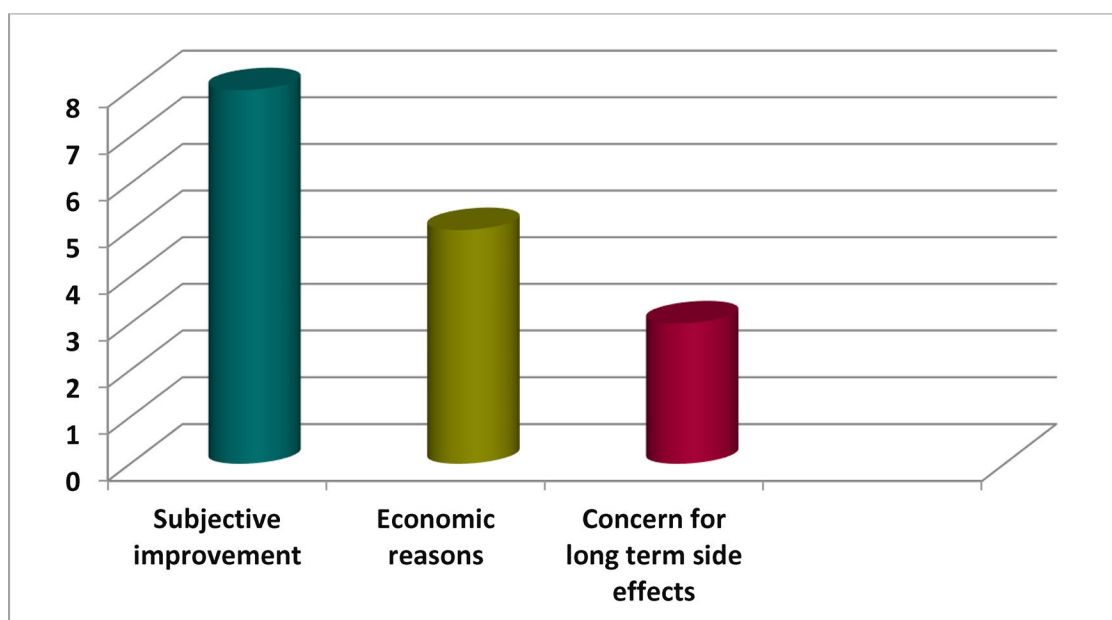


Figure 2. Reasons for discontinuing omalizumab therapy.

cessation of the treatment since the difference in ACT scores at baseline and end of 12 months was significant but the difference at 6 and 12 months (6 months after stoppage of omalizumab) was not statistically significant. The frequency of exacerbations was significantly reduced at 6 months as well as 6 months after cessation of treatment. The frequency of exacerbation was similar at month 6 of therapy and 6 months after cessation of therapy with no significant difference, which indicates that the beneficial effect of omalizumab on decreasing exacerbations was experienced even at 6 months after cessation of treatment. The overall results as depicted in Figure 3 indicate that excellent improvement in asthma control occurs with omalizumab treatment that extends well beyond the duration of therapy.

There was improvement asthma control, maintenance dose of systemic steroids and exacerbation rate after 6 months of omalizumab therapy as compared to the baseline. This improvement was maintained after 6 months of cessation of therapy. The most substantial benefit obtained was with regard to systemic steroid use. All the 16 patients were on maintenance systemic steroids at the beginning of omalizumab treatment. At the end of 6 months of treatment, only 2 patients required maintenance systemic steroids and another 2 patients needed short bursts (5–7 days) of oral steroids for exacerbations. Therefore, omalizumab therapy was successful in 14 patients with regard to weaning them from systemic steroids and none of these 14 patients needed to go back to maintenance steroids at 6 month of post therapy follow-up.

Duration of omalizumab therapy and reasons for discontinuation

16 patients with uncontrolled asthma were given omalizumab therapy. Fourteen out of the 16 patients wanted their clinician to have a finite time point of cessation of therapy even before initiating omalizumab, rather than continuing it for long duration. The mean duration of therapy was 8 months in the treated patients. Most patients (12 out of 16) settled for 6 months of therapy. Two patients continued omalizumab therapy beyond 1 year. No patient had worsening asthma on omalizumab and hence such a reason was not given by any patient for discontinuing omalizumab. The reasons for stoppage of therapy included subjective feeling of improvement, economic constraints and concerns of safety beyond 6 month usage. The subjective improvement was substantiated by an improvement in ACT at 6 months of therapy.

Discussion

Biologic agents have revolutionised the way pulmonologists look at and treat asthma. A combination of inhaled steroids (ICS) with long acting beta two agonists (LABA) has become more or less the standard of care in asthma. Many ICS-LABA combinations are commercially available although recent reviews and systematic reviews (11,12) have highlighted the advantages of formoterol-fluticasone therapy. Patients with severe asthma who remains uncontrolled despite high dose of ICS-LABA merit therapy with biologic

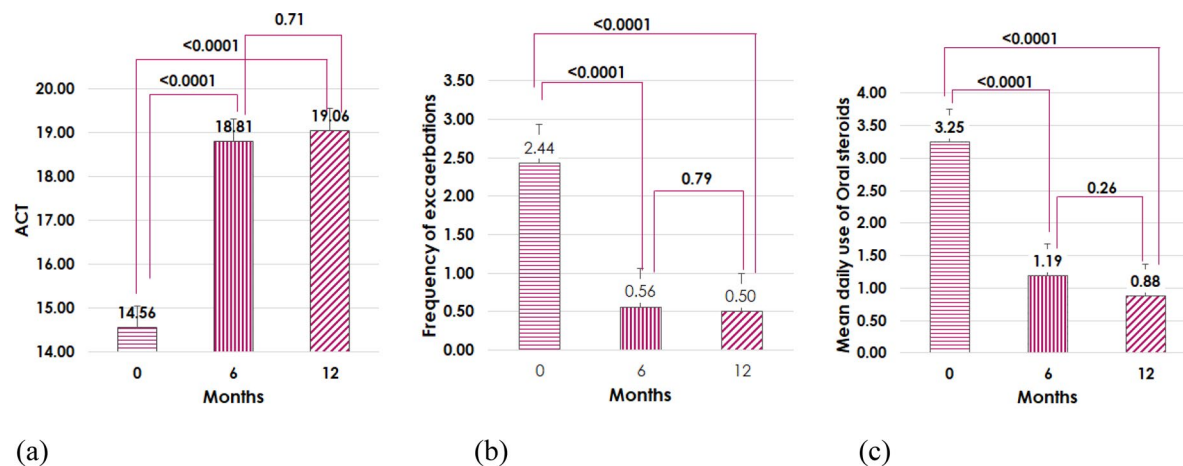


Figure 3. Effect of omalizumab treatment on (a) ACT, (b) frequency of exacerbations (c) use of oral steroids.

agents after evaluation and follow-up from an asthma specialist. Omalizumab, a humanized monoclonal antibody against immunoglobulin E, was the first biologic approved for the treatment of severe allergic asthma. RCTs and real life trials (13–15) have consistently demonstrated its benefit with regard to asthma control and reduction of exacerbations. Treatment with omalizumab is approved for atopic asthmatics within a range of serum IgE levels only. However, there have been reports (16) of its treatment success even in asthmatics with very low IgE and in non atopic asthmatics.

Success of asthma therapy is crucially dependent on treatment adherence, which in turn, is linked to patient beliefs and preference of therapeutic agent. Hence, addressing patient preferences is of paramount importance in asthma treatment. Guidelines have been criticized for not being patient-centric; further guidelines do not address perspectives of multidisciplinary care team involved in patient management. Integrated care pathways (ICPs) are structured care plans involving multiple disciplines that effectively overcome the shortcomings of guidelines. They act as a bridge between guidelines and clinical practice and incorporate evidence based care into protocols and their subsequent translation to patient care. They empower patients to make decisions with choice of therapy. ICPs have become the standard of care in oncology and palliative practice. Similar protocols have been proposed for asthma and other respiratory diseases (17).

As previously mentioned, patient perspectives and attitudes toward biological therapy in asthma has been poorly studied. However, a questionnaire survey (8) looked at real-world thoughts on the prescribing attitudes of primary care physicians, allergists/clinical immunologists, and pulmonologists for the treatment of severe asthma. Seventy-one percent of respondents

advised biologics in place of systemic steroids and felt that biologics are safer than Prednisone at a dose of 5 mg daily. Adherence to global guidelines for identifying severe asthma patients was less than 50%.

REALISE Asia, a questionnaire-based survey of asthmatics (7), put forward five patient-clusters based on asthma control status, attitude toward their asthma and perspectives on asthma therapy. Although this study did not specifically address patient attitude toward biological agents, the observations might have practical implications. The clusters were categorized as

1. Well adjusted – Well-adjusted and asthma at least partly controlled
2. Rejectors – In denial about symptoms
3. Endurers – Tolerating with poor control
4. Lost – Adrift and poorly controlled
5. Worried – Worried with multiple symptoms'

The authors formulated consensus opinions for all attitudinal-control clusters. Pharmacotherapy in 'Rejectors' need to address psychosocial elements contributing to denial of diagnosis and failing to adhere to prescribed treatment. Providing the right quantum of drugs is crucial in 'Endurers' who tend to tolerate symptoms and exhibit lessened ambition to achieve good asthma control. These attitudes make 'Endurers' a potentially at-risk group.

The dropout rate with omalizumab therapy has been addressed in multiple RCTs and real life studies (18–21). In general, the discontinuation has been higher in real life setting. A literature review done in 2016 (22) revealed that the dropout rate in RCTs ranged from 7.1 to 19.4% whereas the real world studies quoted a wide range of discontinuation rate ranging from 0% to 44%. More than half of the real

world studies suggested that patients continued the medication for 12 months or less. Lack of efficacy and concern about adverse effects have been the common reported causes for discontinuation. However, one of the latest real world studies published in 2020 noted more than 90% adherence to 2 year therapy with omalizumab (23). In contrast, our study tends to suggest that excellent clinical control provided by omalizumab therapy makes patients to consider discontinuation. Economic impact of therapy has also been a reason for discontinuation.

There is limited available data on asthma control after discontinuing omalizumab. A prospective study (10) evaluated asthma control in patients continuing or opting out from long-term omalizumab treatment. Higher percentage of patients in the omalizumab group (67%) were exacerbation free compared to the placebo group (47.7%). Time to first exacerbation was prolonged in the omalizumab treated patients, and subjects continuing omalizumab had significantly better asthma control than those who stopped. Another retrospective study from UK (24) looked at patients who were treated with omalizumab for longer than 23 months. Forty-five patients treated for a mean duration of 60 months were evaluated. Eighty percent reduction in the annual acute asthma related hospital admissions, 76.7% reduction in daily mean maintenance OCS dose and clinically significant improvement in asthma control questionnaire were noted which was sustained for a mean period of 60 months. Our study contrasts the observations of these two studies in that the benefits with omalizumab therapy persisted well beyond the duration of therapy, a finding that may be beneficial for patients and policy makers. The 6–8 month of omalizumab therapy could have potentially brought down the allergic response to levels that are controllable by lesser therapies like inhaled steroids and long acting beta two agonists. In similar lines to our study, a real world observational study (25) evaluated 61 patients who discontinued omalizumab therapy after a mean duration of 22.7 months. Sustained control was noticed in a substantial proportion of patients for a period of at least 6 months. Worsening of asthma eventually occurred in 34 patients (55.7%). A median interval between discontinuation and loss of control of 13.0 months was noted. No correlation was detected between time to loss of control and duration of omalizumab treatment. Asthma control tended to be sustained for longer in patients whose patients who had an excellent initial response. In those patients who had worsening asthma symptoms, retreatment with omalizumab failed to evoke benefit in 20%.

Strengths and limitations of the study

Our study is the first in India to have examined patient preferences and attitudes toward omalizumab therapy. Further, it reports, for the first time in India, 6-month real world follow-up data on asthma control after cessation of omalizumab therapy. Our study is a retrospective study with data retrieval from EMR and hence is liable to have some lacunae in information gathered. However, the capturing of data in our difficult asthma clinic is robust with most relevant data being evaluated for and stored. The number of patients who took omalizumab therapy was small and extrapolation to a larger scenario may be challenging. The low numbers of patients who qualify for step 5 treatment may be a testimony to the fact that most patients with uncontrolled asthma have simple modifiable factors as opposed to need for high end treatment like biologicals.

Conclusion

The ARTWORK study reveals some interesting real life observations on omalizumab therapy in India. Sixty-eight percent of deserving and suitable patients with uncontrolled asthma opt out of omalizumab therapy. Unrealistic perception of good asthma control and huge cost of therapy are the commonest causes of rejecting omalizumab therapy. Most patients who opt for omalizumab take the agent for 6–9 months only. Omalizumab renders good asthma control in the real word scenario as evidenced by improvement in asthma scores, lesser need for maintenance systemic steroid therapy and fewer exacerbations. These benefits persist to a significant extent even after 6 months of cessation of therapy. Prospective studies recruiting larger number of patients are needed to replicate and confirm the findings of our study.

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