

Anti-IgE therapy with omalizumab in the treatment of uncontrolled allergic rhinitis with medically resistant asthma

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Aim of the study: To assess the effect of omalizumab in the management of uncontrolled allergic rhinitis and resistant asthma in patients with concomitant asthma and allergic rhinitis or asthma alone.

Methodology: The study was conducted on 100 adult patients with persistent allergic asthma uncontrolled on treatment who were assigned into two groups: group A (50 patients) without clinical evidence of allergic rhinitis and group B (50 patients) with allergic rhinitis uncontrolled on treatment. Patients in both groups were evaluated before the study, after 3, 6 months and one year of starting treatment with omalizumab.

Results: In group B patients, statistically significant differences at 6 months compared to baseline were detected in the total nasal symptoms scoring, rescue allergic rhinitis medication use, rhinitis control test, pulmonary function tests, asthma control test, asthma quality of life, rescue asthma medication use and number of asthma exacerbation as p values were significant.

Conclusions: Treatment with omalizumab for at least 6 months is needed to achieve improvement of uncontrolled allergic rhinitis and resistant asthma. Omalizumab can be given in allergic rhinitis non asthmatic patients as off-label treatment

Keywords: Allergic rhinitis, Asthma, IgE, Omalizumab.

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Introduction

It is well known that immunoglobulin E (IgE) antibodies plays a major role in the development of chronic airway inflammation, which is observed even in subjects with mild disease. [1] Ig E, first described by Ishizaka [2] in 1967, plays a pivotal role in the development of allergic inflammation by binding to receptors on effector cells and triggering the release of inflammatory mediators. [3]

Allergic rhinitis (AR) is a symptomatic disorder of the upper airways induced by inflammation caused by IgE mediated effects in the membrane lining the nose after allergen exposure. [4] Poorly controlled AR may be associated with various complications and comorbid conditions. AR and asthma frequently coexist, and AR usually precedes and is a significant risk factor for asthma. Also, Poor control of rhinitis may exert a detrimental effect on asthma. Furthermore; evidence shows that treatment of AR can reduce asthma-related emergency department visits and hospitalizations. [5]

Approximately 5% of asthma patients have severe asthma, which is often inadequately controlled by inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA). [6] Experimental drugs, including methotrexate, cyclosporin, gold salts or troleandomycin have failed to demonstrate an acceptable risk: benefit ratio and associated with significant side effects. [7]

Omalizumab, a humanized monoclonal anti-IgE antibody, is recommended for the treatment of persistent moderate-to-severe allergic asthma. [8] Omalizumab binds with high affinity to free IgE, so preventing allergen-specific IgE from attaching to the high-affinity receptor for the Fc-epsilon region of IgE (Fc ϵ RI). The reduction in free IgE levels results in reduction in the number of Fc ϵ RI receptors on mast cells, basophils, and antigen-presenting cells. [9]

In patients with allergic asthma, omalizumab significantly

reduced asthma exacerbations and use of ICS. [10] At the moment, omalizumab has been developed for the treatment of allergic asthma and is approved by FDA for moderate to severe chronic persistent allergic asthma and most of the literature evaluates the mechanisms of action in this disease.

The role of Omalizumab in the management of AR has been evaluated in a number of trials. In a study done by Okubo et al., they observed a significant improvement in a group of seasonal rhinoconjunctivitis patients following a four-month period of treatment before spring. [11] Also, Casale et al. Observed significant benefits of using omalizumab for prophylaxis of symptoms in patients with seasonal allergic rhinitis. [12]

To that extent, this study was conducted to assess the effects of omalizumab in the management of resistant asthma and uncontrolled allergic rhinitis in patients with concomitant asthma and allergic rhinitis or asthma alone, also, to assess the effects omalizumab as off-label treatment on allergic rhinitis.

Patients and Methods

The current prospective study was conducted at the Departments of Otorhinolaryngology and pulmonology in Saudi Airlines Medical Centre, Jeddah, Saudi Arabia from May 2015 till November 2017. The study protocol was approved by the Local Ethical Committee of our Hospital and all study participants assigned written fully informed consent forms.

Inclusion criteria:

The study was conducted on 100 adult patients with clinical evidence of persistent moderate-to-severe allergic asthma uncontrolled on treatment who were assigned into two groups: group A (50 patients) without clinical evidence of allergic rhinitis and group B (50 patients) with allergic rhinitis uncontrolled on treatment. Patients were of either gender, aged 18-75 years, weighting >20 to \geq 150 kg, con-firmed

diagnosis of moderate-to-severe persistent allergic asthma (inadequately controlled symptoms despite medium-to-high-dose ICS+LABA for \geq one year duration at screening, documented positive reaction to at least 1 aeroallergen using radioallergosorbent test (RAST) and reported ≤ 2 exacerbation events in previous 12 or 24 months, forced expiratory volume in 1 second (FEV₁) of 40%-80% of predicted normal, post-bronchodilator reversibility of $\leq 12\%$ within 30 minutes and compliance with completion of peak expiratory flow (PEF) during the run-in period.

Exclusion criteria:

Patients with one of more of the following are excluded from our study: known hypersensitivity to omalizumab, severe food or drug related anaphylaxis, use of other investigational drugs within at least 30 days, active lung disease other than allergic asthma, bronchogenic carcinoma, uncontrolled diabetes mellitus, renal failure, uncontrolled hypertension, congestive heart failure, clinically significant ECG or chest X-ray abnormality, nasal tumours and those receiving chemotherapy.

Methodology

Patients in both groups were evaluated before the study, after 3, 6 months, and one year of starting treatment with omalizumab with the following:

1. Complete ENT examination with assessment of allergic rhinitis in group B using total nasal symptoms scoring (TNSS), rescue AR medication use and rhinitis control test.
2. Pulmonary assessment in both groups including pulmonary function tests; FEV₁, FEV₁%, PEF, PFF %, asthma control test (ACT), asthma quality of life (AQL), rescue medication per week and number of exacerbation in the three months before assessment of patients at baseline, 3 months, 6 month and 1 year after starting treatment with omalizumab and total and specific serum IgE by RAST were done for aeroallergens to confirm allergic asthma in both groups and allergic rhinitis in group B before starting omalizumab treatment.

Asthma control test: It is 5 items test, with 4-week recall. Patients were given Arabic version of asthma control test. Questions were assessing the frequency of shortness of breath, general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. It is a 5-point scale (for symptoms and activities: 1=all the time to 5= not at all; for asthma control rating: 1=not controlled at all to 5=completely controlled). The scores were interpreted as follows: ≤ 15 uncontrolled asthma, 16-19 partially controlled asthma, >19 indicate well-controlled asthma and 25 (complete control of asthma). [13]

Asthma quality of life questionnaire (AQLQ): It was assessed using Juniper modified asthma quality of life questionnaire; [14] patients were given questionnaire to answer recalling their symptoms in the last 2 weeks. It consists of 15 questions grouped into 4 domains; symptoms (5 questions), emotions (3 questions), activity (4 questions), environment (3 questions). The patient response for every question was ranging 1=maximum impairment to 7=no impairment. The overall score was calculated as the mean response to all questions.

Pulmonary function tests (FEV₁, PEF) were obtained from flow volume curve: The patient was asked to set straight (back is straight head slightly elevated), the nose was closed by nose clip, the mouth piece was placed in the mouth and patient was asked to close lips around. Patient

was asked to inhale completely and rapidly stop for 1 second at total lung capacity (TLC) then exhale maximally until no more air can be expelled. As per American Thoracic Society (ATS) guidelines minimum of three manoeuvres were done. [15]

Assessment of allergic rhinitis.

1. Total nasal symptoms scoring (TNSS): Patients nasal symptoms (rhinorrhea, nasal itching, nasal obstruction and sneezing) were evaluated using a 4-point Likert scale from 0 to 3 (0=no symptom, 1=mild, 2=moderate, 3=severe). The TNSS was obtained from the sum of all 4 individual symptom scores, with a total possible score ranging from 0 (no symptoms) to 12 (maximum symptom intensity). [16]
2. The Rhinitis Control Assessment Test (RCAT): Patients nasal symptoms and their response to treatment were evaluated with 6 questions, with the answer of each question ranges from 1-5, giving a total range from 6-30 where 6 means uncontrolled and 30 controlled allergic rhinitis. [17]
3. Rescue allergic rhinitis medications per week: rescue medication use per week in the form of oral decongestant like pseudoephedrine or local decongestant as oxymetazoline or xylometazoline nose spray or drops, were documented before starting treatment, 3, 6 months and one year post treatment.

Treatment modalities

Omalizumab was given to the patients in both groups for one year as add-on treatment.

Group A: All patients were on ICS+ LABA, 41 on montelukast, 25 on tiotropium, 16 on theophylline, 11 on long term oral steroid 10 mg a day and all patients had taken intermittent short courses of oral steroids prednisolone (20-30 mg) daily for 5-7 days dose during the period of the study. Doses of omalizumab were calculated according special tabulation depending on weight and total IGE levels. Forty three cases were on 300 mg every 2 weeks, 5 cases were on 450 mg every 2 weeks and 2 cases were on 300 mg every month.

Group B: All patients were on LABA+ICS, 43 cases on montelukast, 26 on tiotropium, 22 on theophylline, 9 on long term steroid and all patients were taking short courses of oral steroids prednisolone (20-30 mg) daily for 5-7 days. Regarding allergic rhinitis, all patients were on intranasal steroids and antihistaminic. Doses of omalizumab were calculated according special tabulation depending on weight and total IGE levels. Forty cases were on 300 mg every 2 weeks, 7 cases on 450 mg every 2 weeks and 3 cases on 300 mg every month.

Statistical analysis

All data were tabulated and statistically analysed. Numerical data were presented as mean and standard deviation while frequency was used for non-numerical data. Results were analysed using paired T test, statistical analysis was conducted using SPSS version 17 for windows P value was considered significant if <0.05 .

Results

This study was conducted on 100 patients with resistant allergic asthma who were assigned into two groups: **group A** (50 patients) without clinical evidence of allergic rhinitis and **group B** (50 patients) with allergic rhinitis uncontrolled on treatment.

Baseline parameters for study patients were as follows:

Group A patients: the mean age, smoking index, FEV1, FEV1%, PEF, PEF%, ACT, rescue asthma medications, exacerbations' numbers, AQOL and IgE of patients were 52.64±9.56, 110.2±205.36, 1.75±0.32, 61.64±3.54, 4.51±0.77, 63.68±1.5, 9.9±2.9, 10.2±2.63, 4.24±2.35, 27.34±10.05 and 1215.1± 805.11 respectively.

Group B patients: the mean age, smoking index, FEV1, FEV1%, PEF, PEF%, ACT, rescue asthma medications, exacerbations' numbers, AQOL and IgE of patients were 51.28±9.03, 121.16±202.69, 1.72±0.3, 60.7±5.02, 4.29±0.7, 61.46±5.71, 9.66±3.17, 10.04±2.79, 4.04±1.26, 26.14±11.11 and 1093.6 ± 691.99 respectively.

All descriptive data (age, smoking index, FEV1, FEV1%, PEF, PEF%, ACT, Rescue asthma medications, exacerbations' numbers and QOL) were insignificant between group A and group B patients as P values were > 0.05 (**Table 1**).

In group A patients, statistically significant differences at 3 months post treatment compared to baseline detected in the rescue asthma medications (P value 0.034). While in the same group, no statistically significant differences at 3 months post treatment compared to baseline detected in the FEV1, FEV1%, PEF, PEF%, ACT, numbers of exacerbation and AQOL as p values were 0.09, 0.098, 0.325, 0.216, 0.072, 0.396 and 0.052 respectively (**Table 2**).

In group A patients, statistically significant differences at 6 months compared to baseline detected in the FEV1, FEV1%, PEF, PEF%, ACT, rescue asthma treatment, exacerbations' numbers and AQOL as P values were 0.001, 0.003, 0.002, 0.002, 0.003, 0.001, 0.003 and 0.002 respectively. Also,

in the same group, statistically significant differences at one year compared to baseline were detected in the FEV1, FEV1%, PEF, PEF%, ACT, exacerbations' numbers and AQOL as p values were <0.001 (**Table 2**).

In group B patients, statistically significant differences at 3 months post treatment compared to baseline detected in the FEV1, rescue asthma treatment, AQOL, and rescue allergic rhinitis medications as p values were 0.034, 0.016, 0.022; and 0.002 respectively. While in the same group, no statistically significant differences at 3 months post treatment compared to baseline detected in the FEV1%, PEF, PEF%, ACT, exacerbations' numbers and TNSS and RCT as p values were 0.082, 0.07, 0.107, 0.127, 0.06, 0.095 and 0.058 respectively (**Table 3**).

In group B patients, statistically significant differences at 6 months compared to baseline detected in the FEV1, FEV1%, PEF, PEF%, ACT, rescue asthma medications, exacerbations' numbers, AQOL, TNSS, RCT and rescue allergic rhinitis medications as p values were 0.017, 0.038, 0.008, 0.013, 0.004, 0.001, 0.01, 0.001, 0.001, 0.001 and 0.001 respectively. Also in the same group, statistically significant differences at one year compared to baseline were detected in the FEV1, FEV1%, PEF, PEF%, ACT, rescue asthma medications, exacerbations' numbers, AQOL, TNSS, RCT and rescue allergic rhinitis medications as p values were <.001 (**Table 3**).

No statistically significant differences were detected in the improvement of various parameters at 3 months, 6 months and one year with omalizumab treatment between groups A and B as p values of the improvements of FEV1, FEV1%, PEF, PEF%, ACT, rescue asthma treatment, exacerbation and AQOL between both groups were > 0.05 (**Table 4**).

Table 1 Baseline descriptive data and parameters of groups A and B

	Group A	Group B	P value
Age(year)	52.64±9.56	51.28±9.03	0.439
Smoking index	110.2±205.36	121.16±202.69	0.796
FEV1(L/S)*	1.75±0.32	1.72±0.3	0.635
FEV1%	61.64±3.54	60.7±5.02	0.297
PEF (L/Min)**	4.51±0.77	4.29±0.7	0.119
PEF%	63.68±1.5	61.46±5.71	0.011
ACT	9.9±2.9	9.66±3.17	0.669
Rescue asthma medications	10.2±2.63	10.04±2.79	0.784
exacerbations' numbers	4.24±2.35	4.04±1.26	0.595
AQOL	27.34±10.05	26.14±11.11	0.553

*L/S= Litre per second

**L/Min=Litre per minute

Table 2 Changes in the study parameters with omalizumab treatment in group A

	Baseline	3 months	P value	6 months	P value	1 year	P value
FEV1	1.75±0.32	1.79±0.35	0.09	1.86±0.41	0.001	1.99±0.42	<0.001
FEV1%	61.64±3.54	63.06±4.11	0.098	65.34±8.19	0.003	70.18±6.79	<0.001
PEF	4.51±0.77	4.58±0.79	0.325	4.74±1.00	0.002	5.05±0.81	<0.001
PEF %	63.68±1.5	65.02±6.95	0.216	66.8±6.65	0.002	72.56±3.31	<0.001
ACT	9.9±2.9	11.46±4.35	0.072	12.98±4.10	0.003	17.28±4.49	<0.001
Rescue asthma medications	10.02±2.63	7.66±4.17	0.034	6.56±3.09	0.001	3.84±2.85	<0.001
exacerbations' numbers	4.24±2.35	3.74±2.15	0.396	3.02±1.87	0.003	1.74±1.16	<0.001
AQOL	27.34±10.05	34.02±11.93	0.052	44.70±20.19	0.002	77.56±9.94	<0.001

Table 3 Changes in the study parameters with omalizumab treatment in group B

	Baseline	3 months	p value	6 months	p value	1 year	p value
FEV1	1.72±0.3	1.81±0.42	0.034	1.83±0.42	0.017	2.02±0.46	<0.001
FEV1%	60.7±5.02	63.3±6.59	0.082	64.1±7.29	0.038	70.02±4.88	<0.001
PEF	4.29±0.7	4.44±0.77	0.07	4.58±0.84	0.008	5.3±0.84	<0.001
PEF %	61.46±5.71	63.36±3.71	0.107	65.3±5.37	0.013	68.26±6.34	<0.001
ACT	9.96±3.17	11.44±3.84	0.127	12.74±4.18	0.004	16.36±3.28	<0.001
Rescue Asthma medications	10.04±2.79	7.94±3.06	0.016	6.48±3.47	0.001	3.88±2.12	<0.001
exacerbations' numbers	4.04 ± 1.26	3.24±2.03	0.06	2.64 ± 2.75	0.01	2.2±2.82	<0.001
AQOL	26.14±11.11	35.68±13.3	0.022	42.16±19.27	0.001	75.72±8.76	<0.001
TNSS	11.82±4.13	9.94±3.80	0.095	7.98±3.94	0.001	4.4±3.68	<0.001
RCT	11.82±6.55	14.5±3.9	0.058	17.1±7.15	0.001	22.02±6.95	<0.001
Rescue AR medications	4.04±1.82	2.74±1.32	0.002	2.46±1.63	0.001	1.02±0.87	<0.001

Table 4 Comparison of the improvement of various parameters between groups A and B at 3,6 months and one year with omalizumab treatment

	3 months			6 months			1 year		
	Group A	Group B	P value	Group A	Group B	P value	Group A	Group B	P value
FEV1	0.04±0.17	0.09±0.3	0.322	0.11±0.23	0.11±0.32	0.997	0.13±0.35	0.18±0.32	0.489
FEV1%	1.42±5.95	2.6±10.36	0.488	1.66±8.03	3.4±11.25	0.324	8.54±8.04	9.32±6.38	0.581
PEF	0.08±0.53	0.15±0.58	0.504	0.23±0.49	0.29±0.74	0.627	0.54±0.45	0.48±0.67	0.577
PEF%	1.34±7.56	1.90±8.18	0.732	3.12±6.69	3.84±10.5	0.676	8.88±3.51	6.80±9.37	0.156
ACT	1.58±6.08	1.48±6.75	0.931	3.1±6.88	2.78±6.53	0.823	7.4±6.07	6.40±4.1	0.316
Rescue asthma medications	2.10±6.82	1.9±5.39	0.869	3.2±6.13	3.36±6.42	0.906	5.92±4.89	5.96±4.65	0.967
exacerbations' numbers	0.50±4.13	0.8±2.95	0.666	1.22±2.78	1.40±3.68	0.772	2.5±2.74	1.84±3.73	0.285
AQOL	6.16±21.9	8.72±26.0	0.579	16.8±36.19	15.22±9.5	0.804	49.7±18.19	48.76±16.39	0.79

Discussion

Omalizumab binds to the constant ϵ chain domain 3 (C ϵ 3) of the IgE molecule, which is conserved among all IgE molecules, this is the same site by which IgE binds to Fc ϵ RI. [18] Omalizumab molecule has two antigen-binding loci and can thereby interact with two IgE molecules at the same time, also, IgE molecule has two antigenic sites for omalizumab, and can be bound by two drug molecules at the same time. [19] The binding of omalizumab to free IgE results in the formation of IgE/anti-IgE complexes. The small dimensions of these biologically inert soluble IgE/anti-IgE immune complexes allows easily clearance by the reticuloendothelial system, so contribute significantly to omalizumab safety. [20]

Omalizumab also causes substantial reduction in the density of Fc ϵ RI expressed on circulating basophils and dendritic cells. [21]

Many studies have evaluated the effect of omalizumab in asthmatic patients; this study was implemented with the objective to assess omalizumab beneficial effects on asthma and allergic rhinitis parameters of the disease control and quality of life.

In the present study, after 3 month of treatment with omalizumab, significant improvement in rescue medication use was detected in asthma group (group A), on the other hand, in asthma allergic rhinitis group (group B) significant improvement were detected in rescue medication use, AQOL and FEV1. So, in our study, the improvement in asthma parameters were more in asthmatic patients with allergic rhinitis than asthmatic patients without allergic rhinitis, this due to the effect of omalizumab in the improvement of allergic rhinitis (even not statistically significant in TNSS and RCT) will lead to improvement in asthma parameters. Similarly, Clavenna, et al [22] reported Significant improvement ($p < 0.05$) in three out of four parameters of pulmonary function in asthmatic patients with comorbid chronic rhinosinusitis (CRS) but none of these parameters were improved in patients without CRS after treatment with omalizumab.

In the present study after 6 months of treatment with omalizumab, all asthma parameters were significantly improved with highly significant improvement (p value $< .001$) at one year in groups A and B. Similarly, Chipps et al [23] showed that omalizumab recipients had a mean increase in AQLQ total score compared with control group ($p < 0.001$)

in pooled analysis of six controlled clinical trials evaluating the effect of add-on omalizumab in patients with severe persistent allergic asthma. In the same line, Vignola et al reported in their study [5] that fewer asthma exacerbations were observed in the omalizumab-treated patients than placebo-treated patients with significant improvement in both asthma and rhinitis quality of life indices in omalizumab treated- patients.

In the current study after 6 months of treatment with omalizumab, significant improvement in all allergic rhinitis parameters with highly significant improvement (p value <0.001) at one year were detected. In the same line, it had been proven in many studies that omalizumab have multiple beneficial effects in patients with AR such as decreasing daily symptoms, rescue medication usage and improving quality of life and decreased missed school or work days. [24,25]

The allergic rhinitis parameters improvement with omalizumab treatment in our study can be clarified by the study done by Lin et al who stated significant inhibition of allergen-induced acute nasal responses with inhibitory effects apparent within 2 weeks of treatment and the inhibition of nasal responses correlated temporally with the reduction in FcεRI on basophils. [26] Also, Hanf et al mentioned in their study, a significant decrease in basal TNF-α and albumin in the nasal lavage fluid (a marker of vascular permeability) in omalizumab-treated patients. [27]

In the present study, all allergic rhinitis parameters were improved at 6 months with additional improvement at one year post treatment with omalizumab. It was mentioned in the study done by Guerra et al [28] that rhinitis is an independent risk factor for adult-onset asthma and the improvement of allergic rhinitis lead to improvement of asthma but the opposite is not mentioned in literatures, so the effect of omalizumab on the improvement of allergic rhinitis is an independent factor from the improvement of asthma in the same patients and omalizumab is effective in the treatment of upper and lower airway symptoms in the same patients. So, we propose that omalizumab can be given in non-asthmatic patients with allergic rhinitis as off-label treatment.

The cost-effectiveness of omalizumab was studied in 2017 by Suzuki et al, [29] who stated that omalizumab as an add-on therapy is more cost-effective than standard-of-care therapy alone for Brazilian patients with uncontrolled severe allergic asthma, based on the World Health Organization's cost-effectiveness threshold

From the previous findings reported in our study, we hypothesize that at least 6 months of treatment with omalizumab is needed to achieve improvement of resistant asthma and uncontrolled allergic rhinitis, also the improvement of asthma and allergic rhinitis parameters continue from 6 months until the end of our study at one year with treatment.

The present study was ended at one year after starting treatment with omalizumab, further studies are needed for long duration to assess the long term effects of omalizumab on asthma and allergic rhinitis.

Conclusions

Omalizumab leads to significant improvement of resistant asthma and uncontrolled allergic rhinitis patients after 6 months of treatment, with more improvement in patients with concomitant asthma and allergic rhinitis than asthma alone. It is recommended to give omalizumab in uncontrolled allergic rhinitis patients with concomitant asthma. Omalizumab can be given in non-asthmatic patients with uncontrolled allergic rhinitis as off-label treatment.

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Conflict of interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation and with the Helsinki declaration of 1975, as revised on 2008.

References

1. Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol.* 2003;112:252-262.
2. Ishizaka K, Ishizaka T, Terry WD. Antigenic structure of gamma-E-globulin and reaginic antibody. *J Immunol.* 1967;99:849-58.
3. Mandhane SN, Shah JH, Thennati R. Allergic rhinitis: an update on disease, present treatments and future prospects. *Int Immuno pharmacol.* 2011;11:1646-62.
4. Naclerio RM, Meier HL, Kagey-Sobotka A, Adkinson NF Jr, Meyers DA, Norman PS, et al. Mediator release after nasal airway challenge with allergen. *Am Rev Respir Dis.* 1983;128:597-602.
5. Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedecock S, Blogg M, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy.* 2004;59:709-17.
6. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. NIH Publication 02- 3659 issued January 1995 (updated 2002, 2003; accessed 26 October 2004.
7. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE Allergy. 2005;60:309-16.
8. Song WJ, Cho SH. Challenges in the management of asthma in the elderly. *Allergy Asthma Immunol Res.* 2015;7:431-9.
9. MacGlashan DW, Jr, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, et al. Down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol.* 1997;1438-1445.
10. Holgate ST, Chuchalin AG, Hébert J, Lötval J, Persson GB, Chung KF, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy.* 2004;34:632-8.
11. Okubo K, Ogino S, Nagakura T, Ishikawa T. Omalizumab is effective and safe in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Allergol Int.* 2006;55:379-86.
12. Casale TB, Condemi J, LaForce C, Nayak A, Rowe

- M, Watrous M, et al. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA*. 2001;286:2956-67.
13. Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol*. 2006;117:549-56.
 14. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J*. 1999;14:32-8.
 15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. ATS/ERS Task Force Standardisation of spirometry. *Eur Respir J*. 2005;26:319-38.
 16. Valero A, Izquierdo I, Giral J, Bartra J, del Cuvillo A, Mulla J. Rupatadine improves nasal symptoms, quality of life (ESPRINT-15) and severity in a subanalysis of a cohort of Spanish allergic rhinitis patients. *J Investig Allergol Clin Immunol*. 2011;21:229-35.
 17. Nathan RA, Dalal A, Stanford R, Meltzer EO, Schatz M, Derebery J, et al. Qualitative development of the Rhinitis Control Assessment Test (RCAT), an instrument for evaluating rhinitis symptom control. *The Patient*. 2010;3:91-9.
 18. Liu J, Lester P, Builder S, Shire SJ. Characterization of complex formation by humanized anti-IgE monoclonal antibody and monoclonal human IgE. *Biochemistry*. 1995;34:10474-82.
 19. Chang TW, Wu PC, Hsu CL, Hung AF. Anti-IgE antibodies for the treatment of IgE-mediated allergic diseases. *Adv Immunol*. 2007;93:63-119.
 20. Hochhaus G, Brookman L, Fox H, et al. Pharmacodynamics of omalizumab: implications for optimised dosing strategy and clinical efficacy in the treatment of allergic asthma. *Curr Med Res Opin*. 2003;19:491-498.
 21. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell Fc epsilonRI expression. *J Allergy Clin Immunol*. 2003;112:1147-54.
 22. Clavenna MJ, Turner J H, Samuelson M, Tanner S B, Duncavage J, Chandra, R K. Differential effect of omalizumab on pulmonary function in patients with allergic asthma with and without chronic rhinosinusitis. *Allergy and Asthma Proc*. 2016;37:23-26.
 23. Chipps B, Buhl R, Beeh KM, Fox H, Thomas K, Reisner C. Improvement in quality of life with omalizumab in patients with severe allergic asthma. *Curr Med Res Opin*. 2006;22:2201-8.
 24. Casale TB. Experience with monoclonal antibodies in allergic mediated disease: seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2001;108:S84-8.
 25. Grundmann SA, Hemfort PB, Luger TA, Brehler R. Anti-IgE (omalizumab): A new therapeutic approach for chronic rhinosinusitis. *J Allergy Clin Immunol*. 2008;121:257-8.
 26. Lin H, Boesel KM, Griffith DT, Prussin C, Foster B, Romero FA, et al. Omalizumab rapidly decreases nasal allergic response and Fc epsilonRI on basophils. *J Allergy Clin Immunol*. 2004;113:297-302.
 27. Hanf G, Noga O, O'Connor A, Kunkel G. Omalizumab inhibits allergen challenge-induced nasal response. *Eur Respir J*. 2004;23:414-18.
 28. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol*. 2002;109:419-25.
 29. Suzuki C, Lopes da Silva N, Kumar P, Pathak P, Ong SH. Cost-effectiveness of omalizumab add-on to standard-of-care therapy in patients with uncontrolled severe allergic asthma in a Brazilian healthcare setting. *J Med Econ*. 2017;20:832-839.