

Effects of omalizumab therapy on allergic rhinitis: a pilot study

S. MASIERI, C. CAVALIERE, E. BEGVARFAJ, D. ROSATI, A. MINNI

Department of Sensory Organs, "Sapienza" University, Rome, Azienda Policlinico Umberto I, Rome, Italy

Abstract. – OBJECTIVE: The use of omalizumab, a humanized monoclonal antibody able to binding Ig-E, is currently authorized only for treatment of severe bronchial asthma. The use of omalizumab in other Ig-E related diseases is off-label, although some studies have provided promising results about it. The aim of this study was to evaluate if therapy with omalizumab in patients affected by asthma and allergic rhinitis has an impact also on allergic rhinitis-related symptoms.

PATIENTS AND METHODS: A longitudinal study was conducted on 11 patients affected by severe asthma and a periodic allergic rhinitis. Patients were treated with omalizumab for 24 weeks with a monthly subcutaneous administration at the dosage recommended by the current guidelines. We observed at the start and at the end of treatment: rhinitis symptoms using the Visual Analogue Scale (VAS); the state of nasal mucosa with fiberoptic nasal endoscopy; airways inflammation by measuring the Fractional Exhaled Nitric Oxide (FeNO); asthmatic symptomatology by means of the Asthma Control Test; the amount of total Ig-E in a blood sample; and the use of symptomatic drugs before and after treatment.

RESULTS: VAS scores to measure general symptomatology and symptoms including nasal obstruction, rhinorrhea, itching and sneezing were significantly reduced. Turbinate hypertrophy was resolved in six of nine patients. Furthermore, eight patients (73%) reduced or eliminated the use of symptomatic drugs.

CONCLUSIONS: Our data confirm the efficacy of omalizumab in the treatment of allergic rhinitis. Controlled studies will now have to be carried out to confirm these preliminary data and will specify indications for a very efficacious but still significantly expensive therapy.

Key Words

Allergic rhinitis, Asthma, Anti Ig-E therapy, Omalizumab.

the world population reaches almost 30%¹. Symptoms are characterized by rhinorrhea, sneezing, itching, nasal obstruction and tearing and may be reversed spontaneously or with drugs². Its impact on quality of life is considerable as allergic rhinitis is an obstacle to social life; it reduces school and work performance and at the same time involves significant costs for specific treatment.

Allergic rhinitis is often associated with bronchial asthma. Over 50% of patients with rhinitis also suffer from asthma, and more than 80% of patients affected by asthma present concomitant rhinitis³. Often, the onset of rhinitis precedes the symptoms of asthma, although the factors responsible for the extension of disorders to the lower airways are still unknown. Moreover, usually the successful treatment of rhinitis improves asthma symptoms, thus reducing the frequency of exacerbations and hospitalization^{4,5}. These epidemiological findings reinforce the assumption according to which allergic rhinitis and bronchial asthma are different components of the same IgE-mediated disease³. The conventional treatment of allergic rhinitis and allergy-related asthma is based on the removal of the responsible allergen, symptomatic treatment with nasal decongestants, antihistaminics, topical corticosteroids and allergen-specific immunotherapy^{6,7}. However, some patients are refractant to conventional therapies.

Omalizumab is an anti Ig-E monoclonal antibody recently approved for the treatment of asthma. It has proven to be very effective in improving the symptoms and reducing the number of exacerbations of this disease⁸.

The aim of this study was to assess if treatment with omalizumab in a group of patients affected by asthma and concomitant allergic rhinitis also influenced the allergic rhinitis-related symptoms.

Introduction

Allergic rhinitis is a pathological condition of the nasal mucosa induced by an IgE-mediated inflammation following allergen exposure. Its incidence is constantly increasing and prevalence in

Patients and Methods

The patients included in the trial were recruited from the Rhinoallergy day hospital of the Otorhinolaryngology Department of the "Sapienza"

University of Rome. Inclusion criteria were: a) diagnosis of a severe form of bronchial asthma with the indication for treatment with omalizumab established by the Italian Drug Authority (AIFA); b) the concomitant presence of allergic rhinitis. The criteria for the prescription of omalizumab are: a) age over 12 years; b) persistent severe allergic asthma with skin tests or *in vitro* reactivity positive for a perennial aeroallergen; c) reduced pulmonary function ($FEV_1 < 80\%$); d) frequent diurnal symptoms or nocturnal awakenings; e) repeated severe asthmatic exacerbations, despite the daily intake of high doses of inhalation corticosteroids plus an inhaled long-acting β_2 -agonist⁹. The diagnosis and evaluation of bronchial asthma severity were made in accordance with GINA guidelines¹⁰, and the diagnosis of allergic rhinitis according to the ARIA guidelines⁵. Patients who presented total serum Ig-E not included between 30 and 1300 IU/ml or body weight > 100 kg were excluded from the trial. The study protocol was approved by the Ethics Committee of the Sapienza University of Rome, and all enrolled patients gave their informed consent.

Omalizumab was administered every four weeks for 24 weeks for a total of 6 doses, in the form of pre-packaged subcutaneous injections, with a variable dose according to the weight of each patient and total serum Ig-E (Table I). The drug did not replace pharmacological therapy prescribed to patients for the treatment of rhinitis and concomitant asthma, but was added to it.

At the beginning of the trial (T_0) and the end of treatment (T_1) we evaluated:

- General clinical conditions and intensity of individual symptoms (nasal obstruction, rhinorrhea, itching, sneezing, tearing) using the Visual Analogue Scale (VAS) with a score ranging from 1 (no symptom) to 10 (worst possible symptom)¹¹.

- The state of nasal mucosa using fiberoptic nasal endoscopy.
- The level of airways inflammation by measuring Fractional exhaled Nitric Oxide (FeNO)¹².
- Asthmatic symptoms using the "Asthma Control Test" questionnaire¹³.
- The level of bronchial obstruction with spirometry (FEV_1).
- Eosinophil and the total IgE amount in a blood sample.

Statistical Analysis

Values are reported as a median (range) or a number (percentage). Proportions were analyzed according to Fisher's exact test and quantitative variables were analyzed with Wilcoxon's test. A value of $p < 0.05$ was considered to be statistically significant.

Results

11 patients were included in the study (7 men and 4 women), aged between 26 and 70 years (mean 47 years), with a weight between 60 kg and 100 kg (mean kg 77). All patients presented sneezing, nasal secretion, nasal obstruction and aqueous rhinorrhea. Following treatment with omalizumab, an improvement of subjective symptomatology and clinical signs of the upper and lower airways was registered. The VAS score for the general clinical status was reduced significantly, with values decreased from 7 (2-8) to 3 (2-5) ($p=0.0125$; Figure 1)

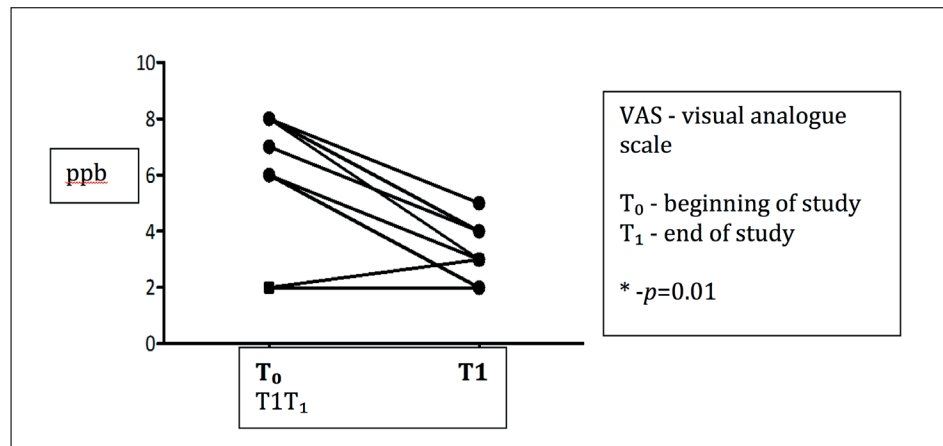
Considering allergic rhinitis, scores for individual symptoms (Table II) decreased in a statistically significant way in all cases except for tearing. At endoscopy, turbinate hypertrophy, which was initially reported in nine patients (81%), was observed in only 3 patients (27%) after the treatment ($p=0.015$); FeNO values also decreased from 56 ppb (10-189) to 43 ppb (10-121) ($p=0.020$; Figure 2).

Table I. Suggested omalizumab dosage.

		Body weight (kg)									
		20-25	25-30	30-40	40-50	50-60	60-70	70-80	80-90	90-125	125-150
Baseline	$\geq 30-100$	75	75	75	150	150	150	150	150	300	300
IgEs (UI/ml)	100-200	150	150	150	300	300	300	300	300	450	600
	200-300	150	150	225	300	300	450	450	450	600	
	300-400	225	225	300	450	450	450	600	600		
	400-500	225	300	450	450	600	600				
	500-600	300	300	450	600	600					
	600-700	300		450	600						
	$\geq 800-1100$										

Administration every 2 weeks

Figure 1. Visual Analogue Scale (VAS) results.



Regarding asthmatic symptomatology, the evaluation of Asthma Control test showed a significant improvement, from 18 (10-20) to 23 (21-25) ($p=0.003$; Figure 3). Also, FEV₁ improved, though not in a statistically significant way ($p=0.236$; Figure 4).

Blood tests showed increased total serum Ig-E from 225 kU/l (36-698) to 747 kU/l (353-2783; $p=0.003$). A reduction in eosinophils was also observed from 8.5 (3.7-14.9) to 4.9 (2.3-12.7; $p=0.074$), although the decrease was not statistically significant.

The pharmacological treatment administered to the patients before and after the utilization of omalizumab is reported in Table III. A reduced intake of drugs was observed in all patients. During treatment with omalizumab, 2 patients out of 11 (18.2%) decided to discontinue all other pharmacological therapy and 6 (54.5%) reduced the number of drugs used. Only 3 (27.3%) continued their usual pharmacological therapy. None of the participants resorted to emergency drugs (SABA, antihistaminics and topical nasal corticosteroids).

No adverse effects were reported in connection with the administration of omalizumab.

Table II. Scores for individual symptoms before (T0) and after (T1) treatment with omalizumab. Values are expressed as a median (range).

SYMPTOM	T0	T1	<i>p</i>
Nasal obstruction	7 (3-10)	3 (2-4)	=0.005
Rhinorrhoea	6 (2-8)	3 (0-4)	=0.007
Sneezing	5 (2-8)	2 (0-4)	<0.003
Itching	3 (0-6)	2 (0-4)	=0.041
Tearing	0 (0-10)	0 (0-6)	=0.067

Discussion

The results of our study show that in patients affected by bronchial asthma and allergic rhinitis, the treatment of asthma with omalizumab has very positive effects also on rhinitis-related symptoms. All symptoms improved and nasal turbinate hypertrophy was completely resolved in most patients. Even FeNO levels (sign of upper and lower airways inflammation) decreased significantly. The efficacy of the therapy was confirmed by the reduced intake of symptomatic drugs by the patients.

Omalizumab is a humanized mouse-derived monoclonal antibody weighing approximately 149 kDa, which binds Ig-E in the part of the molecule, which connects to FCεRI membrane receptors of plasma cells, mast cells, basophils and eosinophils. This prevents binding between Ig-E and effector cells and subsequent phenomena (cell activation, the release of mediators responsible for the allergic response) triggered by the bond between Ig-E and the allergen. In addition to this, omalizumab determines a downregulation of Ig-E production by B lymphocytes¹⁴⁻¹⁶ and of FCεRI production by mast cells and basophils. The inhibition of FCεRI production is also thought to concern dendritic cells, which are involved in the initial allergen sensitization, capturing and processing allergens and then presenting them to the lymphocytes T^{17,18}. Therapy with omalizumab is thus potentially efficacious in all pathologies whose pathogenesis involves a bond between IgEs and effector cells.

During this study, we assessed the effect of anti-IgE monoclonal antibody therapy on allergic rhinopathy, accompanied by bronchial asthma.

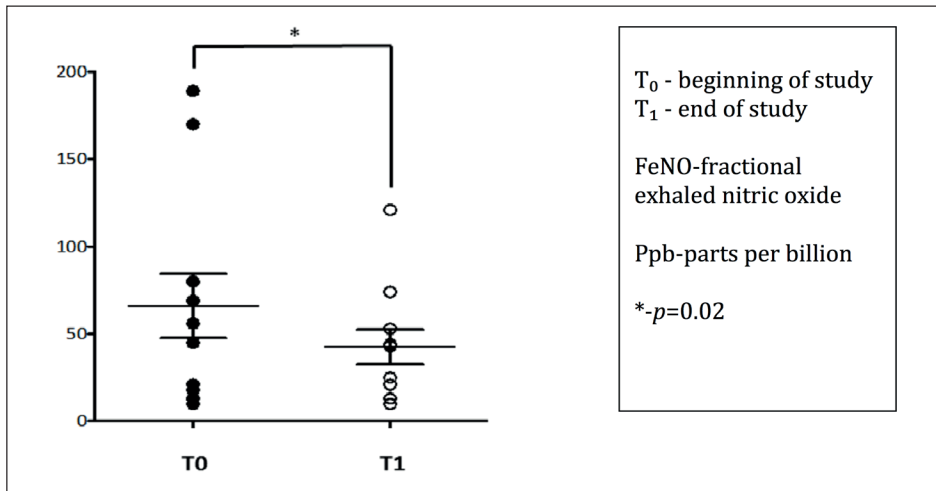


Figure 2. FeNO results.

Figure 3. Asthma control test results.

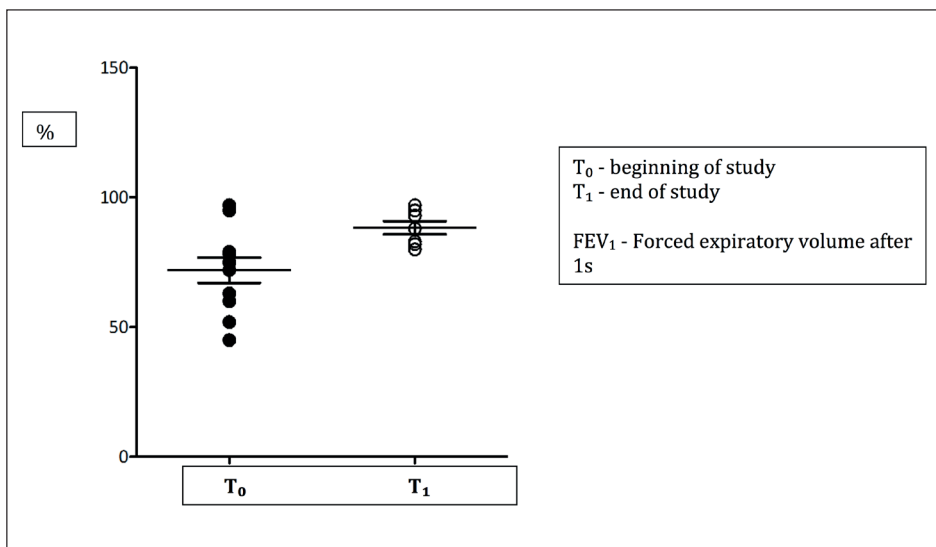
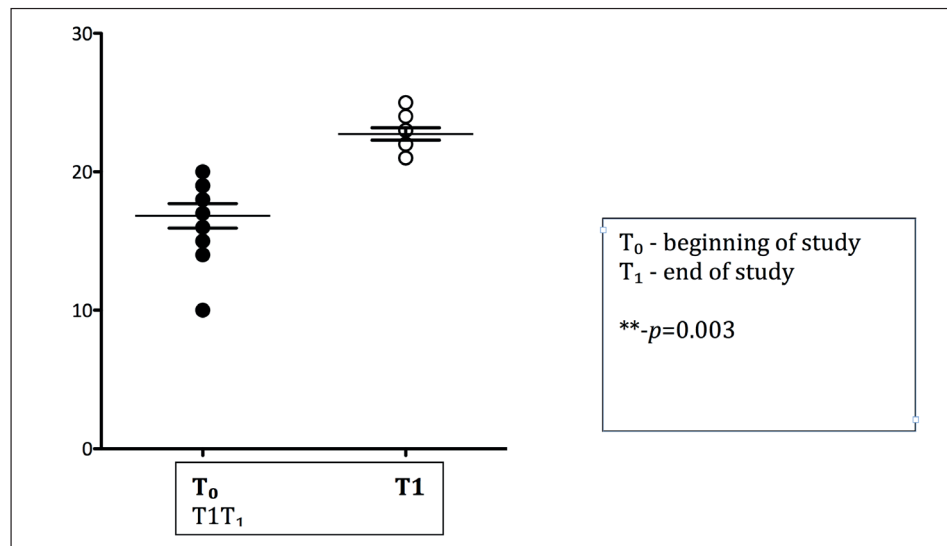


Figure 4. FEV1 results.

Table III. Therapy used by patients treated at T₀ and T₁

Patients	T ₀	T ₁
Pt. 1	ICS+Antileuk+orali CS	ICS+Antileuk
Pt. 2	LABA+ICS+Antileuk Emergency SABA	ICS+Antileuk
Pt. 3	ICS+Antileuk	ICS+Antileuk
Pt. 4	LABA+Antihistaminic Emergency SABA	No therapy
Pt. 5	LABA+Antileuk+SLIT SABA in emergenza	SLIT
Pt. 6	LABA+Antileuk+SLIT Emergency SABA	SLIT
Pt. 7	LABA+Antileuk+SLIT Emergency SABA	SLIT
Pt. 8	LABA+Antileuk+SLIT Emergency SABA	LABA+ Antileuk+ SLIT
Pt. 9	ICS+Antileuk+oral CS	No therapy
Pt. 10	ICS	ICS
Pt. 11	ICS+ Antileuk+oral CS Emergency SABA	ICS

Legend: ICS, Inhaled Corticosteroids; Oral CS, Oral Corticosteroids; SABA, short-acting β_2 agonists; Antileuk, Leukotriene Inhibitors; LABA, long-acting β_2 agonists; SLIT, Sublingual Specific ImmunoTherapy.

This treatment significantly reduced rhinitis-related symptomatology. The positive effect of treatment with omalizumab was confirmed by the decrease in values obtained in the Visual Analogue Scale (VAS), both for the mean group value (VAS T₁=3.3 vs. VAS T₀=5.8), and on the values of individual patients. All patients reported a significant improvement in their general state of health, with an evident enhancement of their quality of life. The symptoms typically characterizing allergic rhinitis as nasal obstruction, rhinorrhea, sneezing, itching and tearing, showed improvement, with a reduction of initial VAS values. The most severe symptom presented by patients at the beginning of the study was nasal obstruction (mean VAS=6.27 with a range of 3-10); this was partly because these patients had been referred to the Rhinoallergy Day Hospital. At the end of treatment, the symptom was reduced, as confirmed by the mean VAS score of 2.9. An improvement was also observed in respect of other symptoms, although with a very slight effect on tearing, even if this symptom was not greatly expressed by our patients. The improvement in symptoms was also confirmed by nasal endoscopy. Endoscopy was performed at the end of the treatment period and it showed an improved state of the nasal mucosa, with a significant reduction in the volume of turbinates and mucous

secretion in the nasal cavities. This improvement could not be related to the fact that the trial was conducted outside the pollen season, because all of our patients were sensitized to perennial allergens (animal hair, dermatophagoides pt, dermatophagoides f.).

Omalizumab also had a good effect on the symptoms related to bronchial asthma. All subjects obtained a higher score in the Asthma Control Test, demonstrating a better control of the disease (ACT T₁=16.8 vs. ACT T₀=22.7). This was confirmed both by increased FEV₁ values, which reflects pulmonary respiratory function, and lower FeNO values, which is a very reliable indicator of eosinophilic airway inflammation¹⁴. In fact the persistence of high FeNO values (normal values 10-25 ppb) despite glucocorticoid therapy, suggests a resistance of inflammation to therapy, while values distributed in the normal range evidently reflect a positive response to treatment¹⁵. Our study did not find a statistically significant correlation between FEV₁ and FeNO values, in agree with previous results reported in the literature¹⁴. Analyzing the values of the systemic inflammation, which occurs during allergic rhinopathy, we observed a significant depletion of serum eosinophils following treatment with the anti Ig-E monoclonal antibody. This finding is consistent with those of other studies about the effect of omalizumab on the eosinophil count¹⁶. The reduction of eosinophilia in peripheral blood reflects omalizumab anti-inflammatory effect¹⁷, which correlates positively with reduced FeNO values, once again confirming that fractional exhaled nitric oxide is a very reliable indicator of eosinophilic inflammation¹⁵.

Most of the literature on the use of omalizumab concerns the therapy of bronchial asthma. A recent Cochrane review¹⁹ showed that in patients affected by severe asthma being treated with corticosteroids, this antibody is effective in preventing asthma attacks, reducing hospitalization and limiting the use of symptomatic drugs. Omalizumab was also used with encouraging but not yet conclusive results in the treatment of some other Ig-E related pathologies, including chronic urticaria, anaphylaxis, food allergy, atopic dermatitis and Allergic bronchopulmonary aspergillosis²⁰. Treatment with omalizumab was also tested on patients affected by allergic rhinitis. In addition to a number of case series, two controlled trials^{21,22} were published on patients affected by seasonal forms, in whom an improvement of symptoms and a lower recourse to symptomatic drugs was observed. Another trial²³ assessed the effects of

the association between omalizumab and specific immunotherapy and observed a quicker attenuation of symptoms. In spite of these encouraging data, however, the indications for this relatively expensive therapy, have to be yet specified according to patient and rhinitis characteristics, as well as optimal dose and mode of administration.

In our study omalizumab was administered at the dose prescribed for bronchial asthma with excellent results on the symptomatology of rhinitis. The dose influences the cost of therapy but even efficacy, because the neutralization of circulating Ig-E depends on the serum concentration of omalizumab. In one of the two controlled trials, the authors tested different dosages. The improvement of symptoms was found to be dose-dependent and was optimal when the monoclonal antibody reached a serum concentration 15 times greater than baseline Ig-E concentration. It should also be observed that the ratio between the concentration reached by omalizumab and that of Ig-E, is influenced by serum Ig-E levels, which vary greatly. In AIFA's guidelines, an exclusion criterion for the treatment of bronchial asthma with omalizumab was particularly low or high Ig-E levels. The pharmacokinetic properties of omalizumab must also be considered: following subcutaneous administration, the serum reaches a plateau in 7-8 days and the half-life of the antibody is about 26 days.

Our findings showed increased total serum Ig-E amount following treatment with omalizumab, from 2 up to 10 times baseline values. This seems to contradict what someone might expect following the administration of an anti Ig-E antibody. Our data agree with those of other studies on this issue. The laboratory method used to measure Ig-E (total and specific) does not distinguish free molecules from molecules binding to the anti Ig-E antibody or to the effector cells (mastocytes and basophils)²⁴. Hamilton et al²⁴ have shown a good correlation between free serum Ig-E and total serum Ig-E before the beginning of treatment with omalizumab, while these two values are no longer correlated after treatment. The Ig-E/omalizumab complex has a longer plasma half-life than that of unbound Ig-E²⁵. This feature determines positive effects. The fragment of Ig-E bound to omalizumab and which binds the antigen (Fab) is still free and may bind allergens, behaving like a competing antagonist of the Ig-E bound to the effector cells¹⁴. For this reason the level of total and specific Ig-E cannot be used to monitor the effect of treatment with omalizumab in daily clinical practice.

The main side effects reported in the literature were a local reaction at the point of injection, diffuse urticarial rashes and anaphylaxis. Omalizumab was well tolerated by all patients in this study, and no adverse events were reported. In particular, no reactions were observed at the point of injection at the time of administration or any time later. In 2007, the omalizumab Joint Task Force (OJTF) recommended that the administration of omalizumab might be preceded by informed consent, adequate information/education on anaphylaxis, the availability of an adrenaline auto-injector, physical examination, and the observation of 30 minutes after the first two shots and two hours after the following injections. Our trial was a preliminary study conducted in a single center. Its limitations derive from the small number of patients and the absence of a control group. At present, the Italian Drug Authority's indications for the use of omalizumab are indeed confined to the treatment of patients affected by bronchial asthma and resistant to normal anti-asthmatic drugs.

Conclusions

Our data suggest that patients treated with omalizumab presented a significant improvement of rhinitis symptoms and a considerable decrease in nasal and bronchial mucosa inflammation. Our data also confirm that the level of total Ig-E cannot be used as an immunity parameter to assess the clinical efficacy of treatment with omalizumab. In the future, the role of omalizumab in the treatment of rhinitis patients will have to be assessed by means of multicentric controlled prospective studies.

Conflict of interest

The Authors declare that they have no conflict of interests.

References

- 1) FRATI F, DELL'ALBANI I, PASSALACQUA G, BONINI S, ROSSI O, SENNA G, INCORVAIA C; Adult SURF Study Group. A survey of clinical features of allergic rhinitis in adults. *Med Sci Monit* 2014; 20: 2151-2156.
- 2) BROZEK JL, BOUSQUET J, BAENA-CAGNANI CE, BONINI S, CANONICA GW, CASALE TB, VAN WIJCK R, OTHA K, ZUBERBIER T, SCHÜNEMANN HJ; Global Allergy and Asthma European Network Grading of Recommendations Assessment, Development and Evaluation Working Group. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; 126: 466-476.

- 3) LEYNAERT B, NEUKIRCH F, DEMOLY P, BOUSQUET J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000; 106: S201-S205.
- 4) TEN BRINKE A, STERK PJ, MASCLÉE AAM, SPINHOVEN P, SCHMIDT JT, ZWINDERMAN AH, RABE KF, BEL EH. Risk factors of frequent exacerbations in difficult-to-treat asthma. *Eur Respir J* 2005; 26: 812-818.
- 5) CORREN J, MANNING BE, THOMPSON SF, HENNESSY S, STROM BL. Rhinitis therapy and the prevention of hospital care for asthma: a case-control study. *J Allergy Clin Immunol* 2004; 113: 415-419.
- 6) PAWANKAR R, MORI S, OZU C, KIMURA S. Overview on the pathomechanisms of allergic rhinitis. *Asia Pac Allergy* 2011; 1: 157-167.
- 7) YIN Q, JIANG WH, WU PQ, HE CH, CHEN RS, DENG L. Clinical evaluation of sublingual administration of dust mite drops in the treatment of allergic asthma and allergic rhinitis of children. *Eur Rev Med Pharmacol Sci* 2016; 20: 4348-4353.
- 8) PELAIA G, VATRELLA A, MASELLI R. The potential of biologics for the treatment of asthma. *Nat Rev Drug Discov* 2012; 11: 958-972.
- 9) Regime di rimborsabilità e prezzo di vendita della specialità medicinale «Xolair» (omalizumab), autorizzata con procedura centralizzata europea dalla Commissione europea. GU Serie Generale n. 279, 2006.
- 10) BOUSQUET J. Global initiative for asthma (GINA) and its objectives. *Clin Exp Allergy* 2000; 30 Suppl 1: 2-5.
- 11) BOUSQUET PJ, COMBESCURE C, NEUKIRCH F, KLOSSEK JM, MÉCHIN H, DAURES JP, BOUSQUET J. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 2007; 62: 367-372.
- 12) LIM KG, MOTTRAM C. The use of fraction of exhaled nitric oxide in pulmonary practice. *Chest* 2008; 133: 1232-1242.
- 13) NATHAN RA, SORKNESS CA, KOSINSKI M, SCHATZ M, LI JT, MARCUS P, MURRAY JJ, PENDERGRAFT TB. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004; 113: 59-65.
- 14) CHANG TW. The pharmacological basis of anti-IgE therapy. *Nat Biotechnol* 2000; 18: 157-162.
- 15) CHANG TW, DAVIS FM, SUN NC, SUN CR, MACGLASHAN DW, HAMILTON RG. Monoclonal antibodies specific for human IgE-producing B cells: a potential therapeutic for IgE-mediated allergic diseases. *Bio-technology (NY)* 1990; 8: 122-126.
- 16) HEUSSER C, JARDIEU P. Therapeutic potential of anti-IgE antibodies. *Curr Opin Immunol* 1997; 9: 805-813.
- 17) MACGLASHAN DW, BOCHNER BS, ADELMAN DC, JARDIEU PM, TOGIAS A, MCKENZIE-WHITE J, STERBINSKY SA, HAMILTON RG, LICHTENSTEIN LM. 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: 1438-1445.
- 18) MACGLASHAN D. Loss of receptors and IgE in vivo during treatment with anti-IgE antibody. *J Allergy Clin Immunol* 2004; 114: 1472-1474.
- 19) NORMANSELL R, WALKER S, MILAN SJ, WALTERS EH, NAIR P. Omalizumab for asthma in adults and children. *Cochrane database Syst Rev* 2014; (1): CD003559.
- 20) ZICARI AM, CELANI C, DE CASTRO G, DE BIASE RV, DUSE M. Anti IgE antibody as treatment of allergic bronchopulmonary aspergillosis in a patient with cystic fibrosis. *Eur Rev Med Pharmacol Sci* 2014; 18: 1839-1841
- 21) CASALE TB, CONDEMI J, LAFORCE C, NAYAK A, ROWE M, WATROUS M, McALARY M, FOWLER-TAYLOR A, RACINE A, GUPTA N, FICK R, DELLA CIOPPA G; Omalizumab Seasonal Allergic Rhinitis Trial Group. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA* 2001; 286: 2956-2967.
- 22) ADELROTH E, RAK S, HAAHTELA T, AASAND G, ROSENHALL L, ZETTERSTROM O, BYRNE A, CHAMPAIN K, THIRLWELL J, CIOPPA GD, SANDSTRÖM T. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000; 106: 253-259.
- 23) KUEHR J, BRAUBURGER J, ZIELEN S, SCHAUER U, KAMIN W, VON BERG A, LEUPOLD W, BERGMANN K, ROLINCK-WERNINGHAUS C, GRÄVE M, HULTSCH T, WAHN U. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. *J Allergy Clin Immunol* 2002; 109: 274-280.
- 24) HAMILTON RG, MARCOTTE G V, SAINI SS. Immunological methods for quantifying free and total serum IgE levels in allergy patients receiving omalizumab (Xolair) therapy. *J Immunol Methods* 2005; 303: 81-91.
- 25) CASALE TB, BERNSTEIN IL, BUSSE WW, LAFORCE CF, TINKELMAN DG, STOLTZ RR, DOCKHORN RJ, REIMANN J, SU JO, FICK RB, ADELMAN DC. Use of an anti-IgE humanized monoclonal antibody in ragweed-induced allergic rhinitis. *J Allergy Clin Immunol* 1997; 100: 110-121.