



Can the response to Omalizumab be influenced by treatment duration? A real-life study



Bruno Sposato^{a,*}, Marco Scalese^b, Manuela Latorre^c, Federica Novelli^c, Nicola Scichilone^d, Manlio Milanese^e, Carmela Olivieri^a, Antonio Perrella^a, Pierluigi Paggiaro^c, on behalf of the Xolair Italian Study Group¹

^a Pneumologia, Ospedale Misericordia, Grosseto, Italy

^b Istituto di Fisiologia Clinica, CNR, Pisa, Italy

^c Cardio Thoracic and Vascular Department, Pathophysiology Unit, University of Pisa, Italy

^d DIMPEFINU, Unit of Pneumology and Medicine, University of Palermo, Palermo, Italy

^e Pneumologia, Ospedale S.Corona, Pietra Ligure, Italy

ARTICLE INFO

Article history:

Received 27 January 2017

Received in revised form

10 March 2017

Accepted 12 March 2017

Available online 14 March 2017

Keywords:

Omalizumab

Severe asthma

Treatment duration

Real-life

Response

Effectiveness

ABSTRACT

Objective: It is unknown whether Omalizumab effectiveness changes over the course of time. Our retrospective real-life study tried to analyze whether Omalizumab response may be influenced by treatment duration.

Methods: 340 severe asthmatics treated with Omalizumab for different periods of time were recruited. They were subdivided into 4 groups according to the Omalizumab treatment length: <12, between 12 and 24, between 24 and 60 and >60 months. Omalizumab treatment results (FEV₁, exacerbations, ACT, SABA use, asthma control levels, medications used and ICS doses) were compared.

Results: ACT, exacerbations, GINA control levels, ICS doses and SABA use were similar in all groups with different Omalizumab treatment durations. Using a linear regression model, corrected for all confounding variables, a higher significant positive increase in FEV₁% in subjects treated for 12–24 ($\beta = 9.49$; $p = 0.034$) or 24–60 months ($\beta = 8.56$; $p = 0.043$) was found when compared with subjects treated for a shorter period. Treatment duration was positively associated with a step down of the other associated therapies (OR: 1.013; $p = 0.019$). This association was more relevant (OR: 4.167; $p = 0.005$) when we considered Omalizumab treatment duration >60 months compared to the shorter therapy. In particular, the percentage of subjects that were taking Montelukast, LABAs and oral corticosteroids was lower in the group treated with Omalizumab for a longer period of time.

* Corresponding author. Pneumologia, Azienda Ospedaliera "Misericordia", Via Senese 161, 58100 Grosseto, Italy.

E-mail address: bsposat@tin.it (B. Sposato).

¹ List of the Investigators of the Xolair Italian Study Group. Sposato B, Migliorini MG, Di Tomassi M, Olivieri C, Perrella A. (U.O.C. Pneumologia, Azienda USLSUDEST, Toscana, Ospedale "Misericordia", Grosseto); Camiciottoli G. (Unità Funzionale Medicina Respiratoria, A.O. Careggi - Firenze); Maselli R, Pelaia G, Busceti M.T. (U.O.C. Pneumologia, Policlinico Universitario Mater Domini - Catanzaro); Sabato E, Cagnazzo M.G. (U.O. Pneumologia, Ospedale Melli - San Pietro Vernotico - Brindisi); Colombo F, Palumbo L. (U.O. Pneumologia, A.O. Ospedale di Circolo e Fondazione Macchi - Varese); Ravazzi A. (Ospedale Sant'Anna - Como); Bucca C. (S.C. Pneumologia, A.O. Città della Salute e della Scienza - Torino); Caiaffa M.F. (U.O. Allergologia e Immunologia Clinica, A.O.U. Ospedali Riuniti - Foggia); Berra A. (SSD Allergologia Respiratoria, Ospedale Giovanni da Procida - Salerno); Calabrese C. (U.O.C. Clinica Pneumologia Sun, Ospedale Monaldi - Napoli); Stanziola A.A. (U.O.C. Pneumotisiologia 1, Ospedale Monaldi - Napoli); Schino P. (U.O.S. Fisiopatologia Respiratoria, Ospedale Miulli, Acquaviva delle Fonti - Bari); Di Gioacchino M. (U.O. Allergologia e Immunologia Clinica, Ospedale SS Annunziata - Chieti); Cazzola M., Segreti A. (U.O.C. Malattie Apparato Respiratorio, Policlinico Tor Vergata - Roma); Pastorello E.A., Scibilia G. (Dipartimento Allergologia e Immunologia, A.O. Ospedale Niguarda Ca' Grande - Milano); Vianello A., Marchi M.R., Paladini L. (U.O.C. Fisiopatologia Respiratoria, A.O. di Padova); Baglioni S., Abbritti M. (U.O. Pneumologia e Unità di Terapia Intensiva, A.O. di Perugia); Almerigogna F., Matucci A., Vultaggio A. (SOD Immunoallergologia, A.O.U. Careggi - Firenze); Maggi E. (SOD Immunologia e Terapie Cellulari, A.O.U. Careggi - Firenze); Maestrelli P., Guarnieri G. (U.O.C. Medicina del Lavoro, A.O. di Padova); Steinhilber G. (U.O. Pneumologia e Fisiopatologia Respiratoria, A.O. Spedali Civili - Brescia); Bonavia M. (U.O. Pneumologia, Ospedale La Colletta - Genova); Rottoli P., Bargagli E. (U.O. Malattie Respiratorie e Trapianto Polmonare, A.O.U. Siena); Senna G., Caminati M. (U.O. Allergologia, A.O.U. Verona); Macchia L. (Unità Dipartimentale di Allergologia e Immunologia Clinica, A.O.U. Policlinico Bari); Bellia V., Scichilone N. (U.O. Malattie apparato Respiratorio 2, A.O. Ospedali Riuniti Villa Sofia-Cervello - Palermo); Paggiaro P., Novelli F., Latorre M., Vergura L. (Sez. Dip. Fisiopatologia Respiratoria e Riabilitazione Respiratoria, A.O.U. Pisana); Masieri S. (Clinica Otorinolaringoiatrica, Policlinico Umberto I, Università di Roma "Sapienza"); Scalese M. (Istituto di Fisiologia Clinica, CNR, Pisa); Rosati Y. (Pneumologia, Ospedale di Macerata); Milanese M. (Pneumologia, Ospedale S.Corona, Pietra Ligure); Folletti I. (Sezione di Medicina del Lavoro, Malattie Respiratorie e Tossicologia Professionale ed Ambientale, Dipartimento di Medicina, Università di Perugia, Az. Ospedaliera Santa Maria, Terni); Pio R., Pio A. (Allergologia e Immunologia Clinica, Ospedale G. Fucito - Mercato S. Severino, Salerno); Maccari U., Maggiorelli C., Scala R. (Pneumologia e UTIP, Ospedale "S.Donato", Arezzo); Vignale L. (Pneumologia, Ospedale di Fivizzano); Pulerà N. (Pneumologia, Ospedale di Livorno); Carpagnano G.E., Foschino Barbaro M.P. (Institute of Respiratory Disease, Department of Medical and Occupational Sciences, University of Foggia, Italy).

Conclusion: In real-life, the positive Omalizumab response remained stable for over 60 months. Long term Omalizumab treatment may lead to a discontinuation of some associated medications and to a slowing down of FEV₁ decline.

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

Omalizumab (Xolair®) is a recombinant DNA-derived humanized monoclonal antibody indicated as an add-on therapy in patients with persistent severe allergic asthma uncontrolled at treatment step 4 or 5 according to guidelines GINA [1]. Both in clinical trials and in real-life studies, Omalizumab showed an improvement in lung function, quality of life, asthma control and a reduction of symptoms, severe exacerbations, healthcare resources, hospitalizations and emergency department visits. It has been also proven to favor a discontinuation of other concomitant asthma medications [2–5]. Several real life studies showed also a benefit after a long term treatment thus suggesting that its effectiveness may persist for a long time [2,6,7]. In fact, studies with follow-ups of about 3–6 years seem to confirm the long term effectiveness of Omalizumab [6,8–11] and, in some cases, showed also a progressive improvement during the course of time [6,7,11].

However, it is still unknown how long the Omalizumab treatment should last. In fact, it is still uncertain whether this drug can have an effectiveness dropout or whether its efficacy remains stable or increases in time. There are no studies specifically designed to evaluate whether the length of Omalizumab treatment can influence its clinical response in time. Therefore, we tried to analyze whether Omalizumab response may be influenced by a different treatment duration in a group of severe asthmatics in therapy with anti-IgE for different periods of time.

2. Materials and methods

This retrospective study considered 340 subjects already recruited for two previous studies [8,9]. All patients were severe allergic asthmatics (step 4–5 treatment level, according to GINA criteria) [1] under Omalizumab treatment for different periods of time (from 4 to 120 months). Omalizumab was prescribed because all patients were affected by severe persistent allergic asthma. Furthermore, they had had a positive skin test or an in-vitro reactivity to a perennial aeroallergen and a reduced lung function (FEV₁ <80%), as well as frequent daytime symptoms or night-time awakenings. These patients had had also multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled β 2-agonist associated to tiotropium and montelukast when possible [1]. Each respiratory center involved in the data collection had to provide a previously agreed form where demographic, clinical and functional data (see previous studies for details) [8,9] were recorded (extracted from patients' clinical records). Also Omalizumab treatment duration was registered at recruitment. Lung function variables (FEV₁, FVC, FEV₁/FVC), Asthma Control Test (ACT), fractional exhaled nitric oxide (FENO), medications used, possible steps down of other concomitant therapies, number of moderate/severe exacerbations, ICS doses and SABA use of rescue medications, observed at the end or during the last year of Omalizumab treatment were also collected and evaluated as responses to anti-IgE therapy. Therefore, subjects were arbitrarily subdivided into 4 groups on the basis of Omalizumab treatment length: subjects in treatment for 1) <12 (39 patients), 2) between 12 and 24 (94 patients), 3) between 24 and 60

(171 patients) and 4) >60 months (36 patients). The variables measured at the beginning of the study, and in particular the results of Omalizumab treatment (FEV₁, exacerbations, ACT, SABA use, asthma control levels, other medications used and ICS doses), were compared among the 4 groups.

3. Statistical analysis

Comparisons of continuous variables among the different groups were performed by using the Kruskal–Wallis test. The categorical variables were compared by either the chi-square test or Fisher's exact test, as appropriate.

Post-hoc comparisons were made by using Bonferroni correction. Linear and logistic binary regression models (all tests with a stepwise forward procedure) were applied when appropriate to evaluate whether there was an association between Omalizumab treatment duration and the response to the therapy in terms of changes in FEV₁, ACT, FENO, number of moderate/severe exacerbations, medications used, ICS doses and SABA use as rescue medication and the level of asthma control. All models were adjusted for age, FEV₁, BMI, various sensitizations, IgE values, Omalizumab doses, comorbidities, smoking habits, age of asthma onset, other treatments (excluding Omalizumab), aspirin intolerance, eosinophils and short-acting bronchodilator responses. The comorbidities considered in the models were: hypertension, diabetes, rhinitis, sinusitis, polyposis, chronic heart diseases, osteoporosis, OSAS, mental disorders gastroesophageal reflux. All calculations were effected by using SPSS software. A $p < 0.05$ was considered as significant.

4. Results

Features of patients, observed before their being treated with Omalizumab, are reported in Table 1. As expected, treatment durations were different among the 4 groups (7 [6–9], 17 [13–20], 41 [33–52], 68 [66–72] months). There were no significant differences among the groups for many anthropometric and clinical data (e.g.: age, BMI, smoking habits, age of asthma onset, asthma familiarity, serum IgE levels, blood eosinophils, bronchodilator response, kind of sensitization, comorbidities). The median monthly dose of Omalizumab in the group treated with this drug for <12 months was higher ($p < 0.01$) in comparison to the other three groups due to the fact that the number of obese subjects was greater in the group with a shorter treatment duration. The number of mono-sensitized and poly-sensitized subjects treated with Omalizumab for <12 months was different ($p = 0.028$) in comparison to the group in treatment with anti-IgE for a period of time between 12 and 24 months. The amount of subjects with rhinitis was lower ($p = 0.028$) in the group treated for a period of time >60 months in comparison to the other three groups. FEV₁% and FEV₁/FVC (evaluated on 125 patients) measured before Omalizumab treatment was similar in all 4 groups.

FEV₁% values measured after a period of time between 12 and 60 months of Omalizumab treatment resulted higher in comparison to values obtained after the shorter period of treatment (Fig. 1 A). FEV₁% values observed after >60 months were slightly lower (not

statistically significant) in comparison to the ones detected in subjects treated for 12–60 months but similar to values measured after the shorter Omalizumab treatment (Fig. 1 A). In patients treated for over 60 months, the mean increase from baseline after a median of 68 month anti-IgE treatment (calculated only in 12 subjects) was 32±58 ml/year. The short-acting bronchodilator response in FEV₁% increase, evaluated in 176 subjects after Omalizumab treatment was similar in all 4 groups: 11.5 [5.2–15], 9 [1–19], 9 [4–18] and 8 [4.5–14.5] in subjects treated for <12, 12–24, 24–60 and >60 months respectively. FVC% was higher in subjects treated with Omalizumab for a period of time between 24 and 60 months, in comparison with those treated for a period of time <12 months (p = 0.03; Fig. 1 B). The number of exacerbations observed in the last year of Omalizumab treatment was similar in all groups (Fig. 2 A). No differences were found in the percentage of subjects with ACT>20 (Fig. 2 B) in all the 4 groups. Also, the number of subjects that used Salbutamol when needed (Fig. 2 C) and with a different asthma control according to GINA guidelines (Fig. 2 D) was similar in all groups. Also FENO (ppb) measured after Omalizumab treatment was similar in all 4 groups (this parameter was evaluated only in 135 patients) (Fig. 3). In addition, ICS doses taken at the end of the Omalizumab treatment were similar in all 4 groups, although

a decrease trend in dosages was observed (Fig. 4 A). On the contrary, the percentage of subjects that showed a treatment step down (excluding Omalizumab) at the end of the treatment period was higher in the group that had taken anti-IgE for a period >60 months when compared to subjects that had been treated for a shorter period of time (p = 0.033; Fig. 4 B). When treatments were analysed separately, we found that the percentage of subjects that had taken Montelukast, LABAs and oral corticosteroids (OCS) was lower in the group treated with Omalizumab for a longer period of time (Fig. 4 C).

When we applied a linear regression model (corrected for all confounding variables), we did not find any associations between Omalizumab treatment duration (considered in months as continuous variable) and FEV₁% measured at the end of treatment with anti-IgE (Table 2). The same was found for the ACT and FENO. On the contrary, we found (still using a linear regression model corrected for all confounding variables), a significantly greater increase in FEV₁% in subjects treated with Omalizumab for 12–24 (β = 9.49; p = 0.034) or 24–60 months (β = 8.56; p = 0.043), in comparison with subjects treated for a shorter period when time was considered as a categorical variable (Table 2). On the contrary, no significant changes in FEV₁% were found in subjects that had

Table 1
Baseline characteristics of patients.

	≤12 months of treatment (n. 39)	>12 and ≤24 months of treatment (n. 94)	>24 and ≤60 months of treatment (n. 171)	>60 months of treatment (n. 36)	p
Age	51 [42–64]	51 [40–61]	54 [46–62]	53 [44–63]	0.067
Males	17 (43.6%)	33 (35.1%)	56 (32.7%)	15 (41.7%)	0.516
Months of Omalizumab treatment	7 [6–9]	17 [13–20]	41 [33–52]	68 [66–72]	<0.001
BMI	27.16 [24.6–32.3]	25.96 [23–28.5]	26.64 [24.1–29.8]	26.4 [23.17–28.79]	0.070
Underweight subjects	–	5 (5.3%)	2 (1.2%)	–	0.114
Normal weight subjects	11 (28.2%)	33 (35.1%)	51 (29.8%)	15 (41.7%)	
Overweight subjects	15 (38.5%)	42 (44.7%)	76 (44.4%)	13 (36.1%)	
Obese subjects	13 (33.3%)	14 (14.9%)	42 (24.6%)	8 (22.2%)	
Smokers	11 (28.2%)	27 (29%)	34 (20%)	9 (25%)	0.228
Ex-Smokers	1 (2.6%)	10 (10.8%)	9 (5.3%)	3 (8.3%)	
Non-smokers	27 (69.2%)	56 (60.2%)	127 (74.7%)	24 (66.7%)	
Pack year (ex and actual smokers)	16.9 [4–26.8]	10 [4–20]	10 [7–20]	10 [5–20]	0.781
Age of asthma onset (yrs)	29 [10–40]	27 [15–40]	30 [18–40]	22 [7–41]	0.512
Familiarity for asthma	15 (38.5%)	41 (59.4%)	63 (41.2%)	12 (46.2%)	0.062
Total serum IgE UI/ml	432 [218–636]	368 [153–600]	292 [169–470]	286 [163.5–478.5]	0.208
Monthly Omalizumab dose (mg)	600 [450–900]*	450 [300–750]*	450 [300–600]*	300 [300–600]*	0.03
FEV ₁ % pre-Omalizumab ^a	64 [55–76.6]	69 [58–75]	70 [58–78]	61.7 [41.8–68.5]	0.111
FEV ₁ /FVC pre-Omalizumab ^a	57 [53–65]	55.6 [50–68]	61.8 [54–71]	54 [47–60]	0.109
Blood eosinophils n/mm ³	242.3 [106–570]	260 [140–420]	261 [85–428.4]	300 [120–360]	0.961
No of subjects with blood eosinophils >3%	21 (70%)	26 (65%)	55 (59.8%)	11 (68.8%)	0.723
ASA sensibilization	7 (18.4%)	16 (23.9%)	33 (22%)	6 (21.4%)	0.935
House dust mite	30 (78.9%)	79 (88.8%)	140 (88.1%)	27 (75%)	0.103
Pollens	19 (51.4%)	59 (68.6%)	99 (64.3%)	21 (60%)	0.315
Moulds	3 (8.1%)	11 (12.9%)	24 (15.6%)	4 (11.4%)	0.649
Cat/dog dander	10 (26.3%)	24 (28.2%)	48 (30.4%)	8 (22.2%)	0.785
Mono-sensitized (to 1 allergen)	21 (55.3%)*	27 (30.3%)*	55 (34.6%)	17 (47.2%)	0.028
Poly-sensitized (≥2 allergens)	17 (44.7%)*	62 (69.7%)*	104 (65.4%)	19 (52.8%)	
No of subjects with rhinitis (%)	26 (66.7%)	64 (69.6%)	118 (69.8%)	16 (44.4%)*	0.028
No of subjects with sinusitis (%)	12 (31.6%)	23 (26.1%)	69 (41.6%)	13 (37.1%)	0.098
No of subjects with nasal polyposis (%)	9 (23.7%)	19 (20.9%)	45 (26.8%)	5 (14.3%)	0.390
No of subjects with 0 comorbidity (%)	17 (43.6%)	34 (37%)	45 (26.6%)	11 (30.6%)	0.068
No of subjects with 1 comorbidity (%)	6 (15.4%)	30 (32.6%)	43 (25.4%)	11 (30.6%)	
No of subjects with ≥2 comorbidities (%)	16 (41%)	28 (30.4%)	81 (47.9%)	14 (38.9%)	

Post-hoc comparisons were made by Bonferroni correction.*the monthly dose of Omalizumab in the group treated with this drug for <12 months was higher (p < 0.01) in comparison to other three groups. Obviously the duration of treatment were different in all groups when compared among them. Mono-sensitized and poly-sensitized subjects treated with Omalizumab for <12 months was different (p = 0.028) in comparison to the group in treatment with the same drug for a period of time of 12–24 months. Subjects with rhinitis in the group treated with Omalizumab for a period of time >60 months were lower (p = 0.028) in comparison to other three groups. Comorbidities considered were: hypertension, diabetes, chronic heart disease, osteoporosis, OSAS, mental disorders, gastroesophageal reflux.

^a Evaluated on 125 patients where values before Omalizumab was collected.

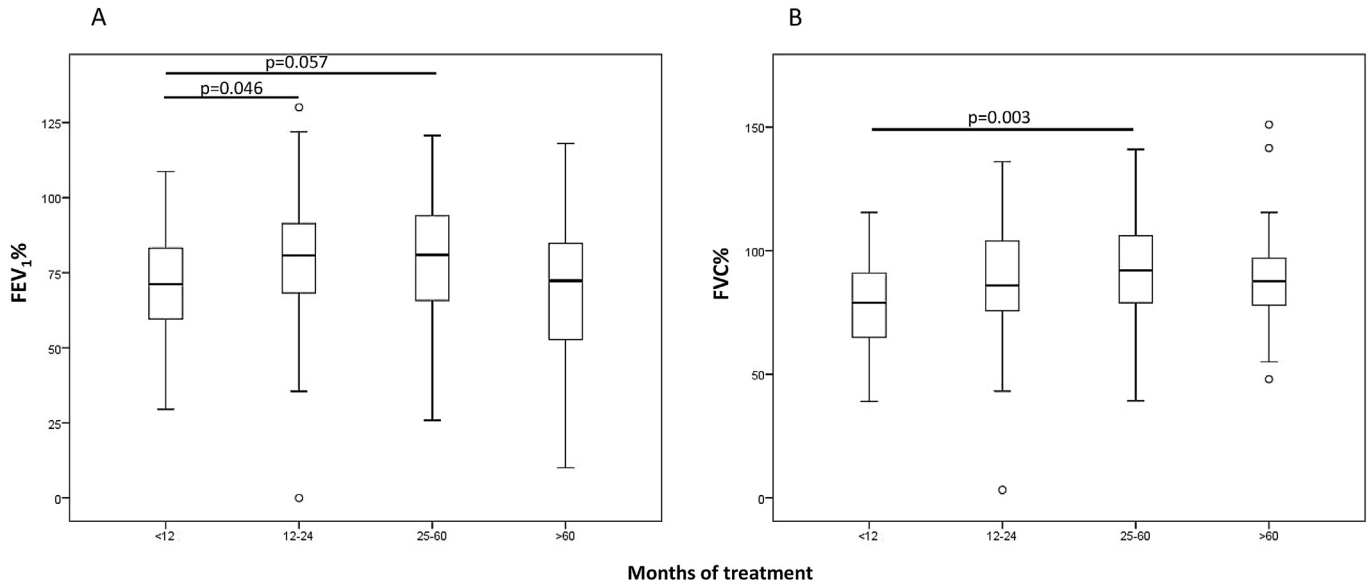


Fig. 1. FEV₁% (A) and FVC% (B) measured in the 4 groups at the end of different periods of Omalizumab treatment. Only significant p values were reported in figures. Group treated for <12 months vs group treated for over 60 months: $p = 0.7$ for FEV₁% and $p = 0.8$ for FVC%.

been treated both for a shorter and a longer period of time (Table 2). No relationships were found among FENO, ACT and different durations of treatment considered.

Furthermore, by using logistic models (corrected for all confounding variables), we did not find any influences of Omalizumab treatment duration on exacerbations, ACT, SABA use, asthma control levels and ICS dosages observed at end of each treatment period (Table 3). On the contrary, treatment duration (months) was positively associated to a step down of other therapies (OR: 1.013; $p = 0.019$). This association was greater (OR: 4.167; $p = 0.005$) when

we considered an Omalizumab treatment duration >60 months compared to a shorter therapy.

5. Discussion

According to our study in a real life setting, the response to Omalizumab did not appear to be influenced by treatment duration. In fact, the main asthma outcomes after Omalizumab (ACT, exacerbations, GINA control, ICS doses and SABA use) were similar in subjects treated for less than 1 year and over 60 months.

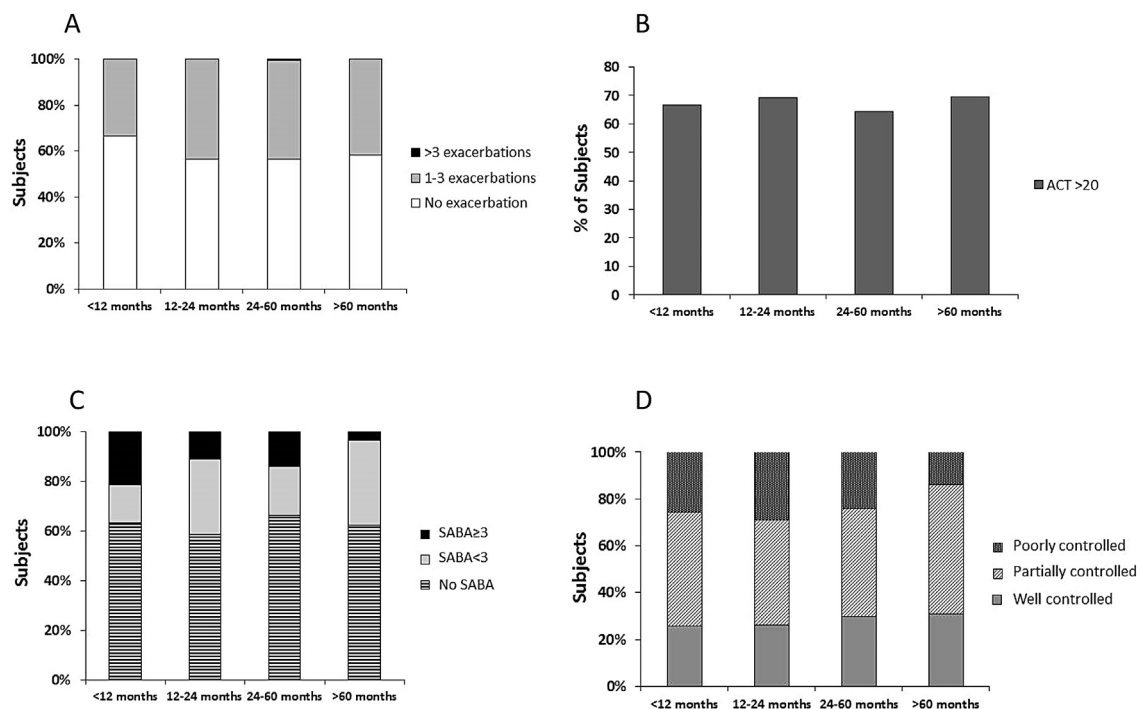


Fig. 2. Percentage of subjects with different number of exacerbations (A), ACT >20 (B), SABA usage (C) and asthma control levels according GINA guidelines (D), observed in the 4 groups at the end of different periods of Omalizumab treatment. No differences were found both among 4 groups and various sub-groups for all variables considered.

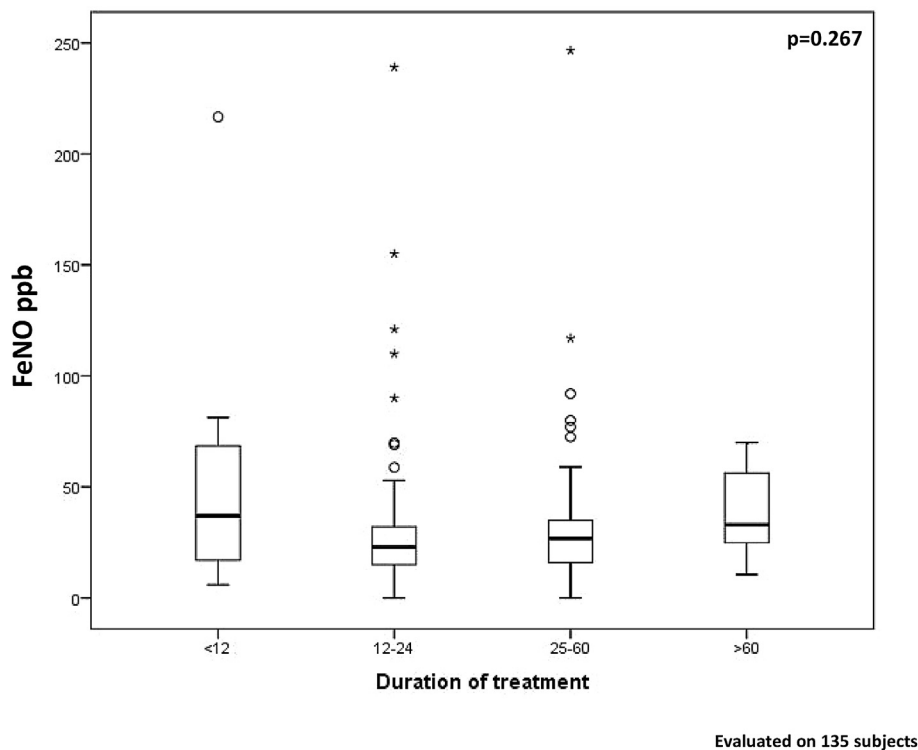


Fig. 3. FeNO value observed in the 4 groups at the end of different periods of Omalizumab treatment. No differences were found among 4 groups: $p = 0.267$.

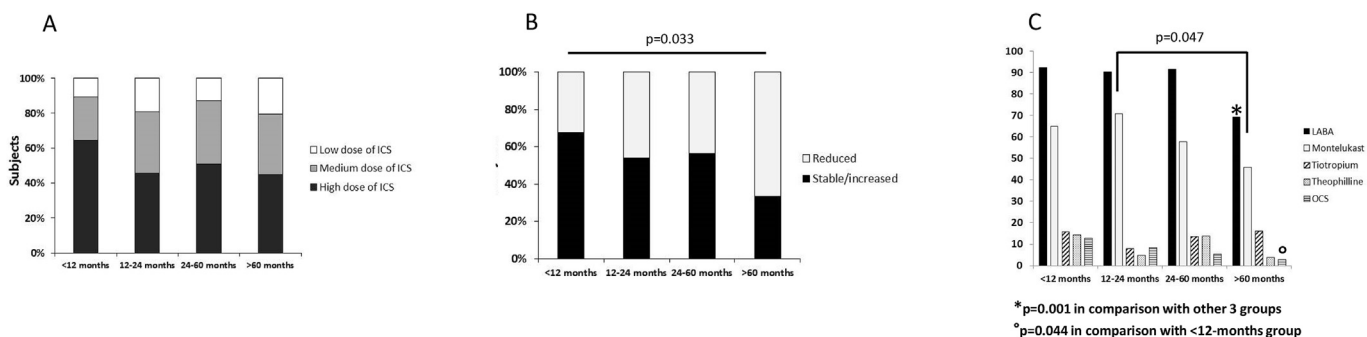


Fig. 4. Percentages of subjects that used different doses of ICS (A) and showed a reduced (step down) or stable/increased therapy level (B) and percentages of patients in the 4 groups that had taken various medications at the end of different periods of Omalizumab treatment. No differences were found both among 4 groups and various sub-groups for all variables considered. Only significant p values were reported in figures B and C.

Furthermore, there was no association between Omalizumab treatment length and ACT response rate, number of exacerbations, GINA control, ICS doses and SABA use when patients were evaluated without any confounding factors. Such result suggests that Omalizumab effectiveness can be seen even during the first months

of treatment and that it persists unchanged during the course of time. These findings are in line with what found by other authors, on data obtained from different observational studies, that highlighted how ACT improved rapidly and significantly after the first year and then progressively, even if slightly, during the following

Table 2

Linear regression models among various asthma outcomes assessed at the end of the period considered and the duration of Omalizumab treatment (evaluated both as continuous and categorical variables).

	FEV1% (β)	p	ACT (β)	p	FeNO (β)	p
Treatment duration (months)	−0.083	0.177	0.008	0.45	−1.53	0.39
12-24-months treatment duration (vs <12 months)	9.49	0.034	0.50	0.492	−13.02	0.234
24-60-months treatment duration (vs <12 months)	8.56	0.043	0.43	0.524	−15.43	0.148
>60 months treatment duration (vs <12 months)	−1.89	0.735	1.04	0.239	−9.74	0.581

For each value a linear regression model was applied. Each model was adjusted for age, FEV₁, BMI, various sensitizations, IgE value, Omalizumab dose, comorbidities (considering separately: hypertension, diabetes, rhinitis, sinusitis, nasal polyposis, chronic heart disease, osteoporosis, OSAS, mental disorders, gastroesophageal reflux), smoking habits, age of asthma onset, ICS dose, LABA use, Montelukast use, aspirin intolerance, eosinophils, short-acting bronchodilator response.

4–5 years [6,7], confirming the continuous effectiveness of Omalizumab in time. We did not find any withdrawal or dosage reduction of ICS contrariwise of what observed by other authors [4,5,11,12]. Conversely, we found a higher percentage of subjects that showed a reduction of the associated treatment level (step down) when the anti-IgE therapy was protracted for over 60 months. In particular, a significantly lower number of subjects took LABA and Montelukast after a treatment of more than 60 months. Also when data analysis was adjusted for all confounding factors, the long term Omalizumab treatment was associated to a reduction of the other concomitant therapies. Also the number of subjects that had taken oral corticosteroids decreased when Omalizumab was taken for a longer period thus confirming what found by other researchers [13–15]. This reduction in the use of other additional drugs after a long-term treatment is an indirect sign of a progressive asthma control improvement over the course of time. Probably, the protracted stabilization of such control, by using Omalizumab continuously, may lead to the progressive discontinuation of some concomitant medications. Such result might suggest a possible regression of the asthma severity level with a continuous anti-IgE treatment in time. Furthermore, these observations suggest that anti-IgE treatment should be effected continuously over the course of time as a maintenance therapy. In fact, Omalizumab cessation has resulted in symptom recurrence [13,16–18]. Therefore, it should be recommended not to stop this drug and to promote adherence to treatment considering that in real-life studies Omalizumab drop-out rate can reach 45.5% [19]. Consequently, a continuous treatment may lead to a progressive cost reduction for asthma management not only due to healthcare resource utilizations, hospitalizations, emergency department visits but also to the reduction or discontinuation of other asthma medications [2,3,20,21].

We also observed that the FEV₁% value measured after treatment was significantly higher in subjects treated for 12–60 months, in comparison with the value measured in patients treated for a shorter period. Furthermore, also adjusting for all confounding factors, a higher significant FEV₁% value increase after treatment was observed in groups treated for 12–60 months when compared with the group that had taken Omalizumab for a period <12 months. These results would lead us to hypothesize that Omalizumab may progressively improve FEV₁% during the first year of treatment, reaching a possible effectiveness peak during the following 12–60-month period of therapy and then stabilizing or slightly decreasing in the following months. In fact, some studies performed for only 4–6 months, showed a FEV₁ increase of about 10% after Omalizumab [22,23], whereas, others highlighted that FEV₁ improvement could reach values up to 15–24% after 3–4

years of Omalizumab [9,11,24,25] suggesting a possible time dependent effect of anti-IgE treatment. However, to date, there are not specific studies on this topic.

We also noticed that FEV₁ measured after a treatment for over 60 months, although in downward trend from the peak observed in the period between 12 and 60 months, was similar to what detected in subjects treated for shorter periods. Furthermore, an unchanged response to short-acting bronchodilator at the end of all period of Omalizumab treatment and a positive change in FEV₁ from baseline was observed in some patients even after a treatment for over 60 months (+32±58 ml/year). On the contrary, according to a recent study, in subjects with severe asthma not treated with Omalizumab but only with a combination of inhaled corticosteroids and LABA for a median of 8 years, FEV₁ change (decline) was –27.1 (–51.1–1.4) ml/year [26]. Therefore, since the period of our observations was very long, these results lead us to suppose that long-term Omalizumab treatment may also have an effect on slowing-down/stopping lung function decline positively influencing the inflammation induced airway remodeling. Unfortunately, this study was not designed to evaluate FEV₁ decline because of the lack of lung function repeated measurements. This did not permit to calculate a precise pulmonary function loss. In fact, we do not know if long-term treated patients (>60 months) could have shown a higher FEV₁ peak during the first years and then a possible progressive reduction throughout the following years. However, as already reported above, also other studies, conducted for 3–4 years, reported an increase of FEV₁ after anti-IgE treatment up to 15–24% [9,11,24,25], confirming a long-term persistence of lung function improvement after Omalizumab therapy protracted for a long period. Therefore, a long-term Omalizumab treatment may positively influence lung function decline. We know that severe asthmatics have a greater decline in lung function over time than subjects with mild-to-moderate asthma [27,28]. We also know that several annual severe exacerbations characterize severe asthma phenotype and that these exacerbations are associated to a more accelerated FEV₁ decline [29,30]. In fact, asthma exacerbations could have long-term adverse structural and functional airway changes thus influencing lung function decline [27]. Therefore, Omalizumab, reducing efficaciously the number of exacerbations, may indirectly reduce structural changes induced by intermittent periods of worsening airway inflammation, thus slowing down lung function decline. We also know that dose-dependent IgE induces proliferation of airway smooth muscle cells and favors extracellular matrix and collagen deposition (collagen-type-I, -III, -VII and fibronectin), thus increasing airway remodeling in asthma [31,32]. Blocking IgE action, by using Omalizumab, prevents all aspects of airway remodeling inhibiting both airway smooth

Table 3

Logistic regression models of Omalizumab treatment durations on various asthma outcomes (measured at the end of each period of time considered).

	No exacerbations (vs at least 1 exacerbation)	ACT>20 (vs <20)	No SABA use (vs use of SABA)	Well control (vs partial/poor control) ^a	Step down of therapy (vs unchanged/stepped up treatment) ^b	Low dose of ICS (vs medium/high dose of ICS)
Treatment duration (months)	OR = 1.010 p = 0.091	OR = 0.994 p = 0.431	OR = 1.00 p = 0.94	OR = 1.00 p = 0.393	OR = 1.013 p = 0.019	OR = 1.00 p = 0.712
12-24-months treatment duration (vs <12 months)	OR = 2.150 p = 0.070	OR = 0.832 p = 0.719	OR = 1.371 p = 0.485	OR = 0.758 p = 0.555	OR = 1.773 p = 0.164	OR = 1.995 p = 0.301
24-60-months treatment duration (vs <12 months)	OR = 1.80 p = 0.135	OR = 0.708 p = 0.467	OR = 0.958 p = 0.918	OR = 1.069 p = 0.876	OR = 1.610 p = 0.218	OR = 1.247 p = 0.738
>60 months treatment duration (vs <12 months)	OR = 1.779 p = 0.254	OR = 0.803 p = 0.751	OR = 1.149 p = 0.792	OR = 1.868 p = 0.346	OR = 4.167 p = 0.005	OR = 2.174 p = 0.309

For each variable a logistic model was applied. Each model was adjusted for age, FEV₁, BMI, various sensitizations, IgE value, Omalizumab dose, comorbidities (considering separately: hypertension, diabetes, rhinitis, sinusitis, nasal polyposis, chronic heart disease, osteoporosis, OSAS, mental disorders, gastroesophageal reflux), smoking habits, age of asthma onset, ICS dose, LABA use, Montelukast use, aspirin intolerance, eosinophils, short-acting bronchodilator response (when appropriate).

^a According GINA guidelines.

^b Except Omalizumab.

muscle cells proliferation and deposition of pro-inflammatory collagens and fibronectin [31–33]. This was confirmed also by Riccio et al. who found a reduction of reticular basement membrane thickness shown by bronchial biopsies after one year of anti-IgE treatment [34]. Also Hoshino et al. found that, after 16 weeks, Omalizumab reduced airway wall thickness measured by using computed tomography [35].

Another aspect highlighted by this study was the increase/stability in FVC % with a long term Omalizumab treatment when compared to patients treated for a shorter period. This is in line with what found by other authors [11]. The increase in FVC may be an indirect sign of small airway function improvement/stability, suggesting a possible and specific role of Omalizumab in treating distal airway inflammation. In fact, a study highlighted an improvement of alveolar nitric oxide levels after Omalizumab, a marker of small airway impairment [36]. Besides, uncontrolled small airway inflammation is related to airway remodeling and disease progression with a more rapid lung function decline [37]. Therefore, a possible action of Omalizumab, at the level of small airways, may also favorably influence the course of the disease in time reducing lung function decline.

An important message of this study is that Omalizumab, maintaining its effectiveness unchanged even after a very long period of time, should be considered as a maintenance treatment over time in severe asthma. Furthermore, the step down of concomitant medications associated to Omalizumab therapy occurring during a long-term treatment, associated to a possible slowing down of lung function decline, would suggest that a continuous use of Omalizumab could make asthma less severe over the course of time, thus modifying the natural history of such disease. In the future, perhaps, we will use Omalizumab precociously for early asthma, thus improving, probably, the prognosis of the disease.

In conclusion, the response to Omalizumab does not seem to be influenced by the duration of treatment even after an over 60 month period. A long-term therapy may also lead to a reduction/withdrawal of other combined medications and may have a protective effect on FEV₁ decline in severe asthma. Omalizumab should be considered as a continuous severe asthma treatment over time.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

- [1] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, Updated 2016. Available at: <http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/> [accessed January 2017].
- [2] I. Abraham, A. Alhossan, C.S. Lee, H. Kutbi, K. MacDonald, "Real-life" effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review, *Allergy* 71 (2016) 593–610.
- [3] M. Caminati, G. Senna, M. Guerriero, A.R. Dama, F. Chieco-Bianchi, G. Stefanizzi, et al., Omalizumab for severe allergic asthma in clinical trials and real-life studies: what we know and what we should address, *Pulm. Pharmacol. Ther.* 31 (2015) 28–35.
- [4] T. Lai, S. Wang, Z. Xu, C. Zhang, Y. Zhao, Y. Hu, C. Cao, S. Ying, Z. Chen, W. Li, B. Wu, H. Shen, Long-term efficacy and safety of omalizumab in patients with persistent uncontrolled allergic asthma: a systematic review and meta-analysis, *Sci. Rep.* 5 (2015) 8191.
- [5] R. Normansell, S. Walker, S.J. Milan, E.H. Walters, P. Nair, Omalizumab for asthma in adults and children, *Jan, Cochrane Database Syst. Rev.* 13 (1) (2014) CD003559.
- [6] J.L. Zazzali, K.P. Raimundo, B. Trzaskoma, K.E. Rosén, M. Schatz, Changes in asthma control, work productivity, and impairment with omalizumab: 5-year EXCELS study results, *Allergy Asthma Proc.* 36 (2015) 283–292.
- [7] W. Storms, M.S. Bowdish, J.R. Farrar, Omalizumab and asthma control in patients with moderate to-severe allergic asthma: a 6-year pragmatic data review, *Allergy Asthma Proc.* 33 (2012) 172–177.
- [8] F. Novelli, M. Latorre, L. Vergura, M.F. Caiaffa, G. Camiciottoli, G. Guarnieri, et al., Xolair Italian Study Group, Asthma control in severe asthmatics under treatment with omalizumab: a cross-sectional observational study in Italy, *Pum Pharmacol. Ther.* 31 (2015) 123–129.
- [9] B. Sposato, M. Scalese, M. Latorre, N. Scichilone, A. Matucci, M.6 Milanese, S. Masieri, G. Rolla, G. Steinhilber, Y. Rosati, A. Vultaggio, I. Folletti, S. Baglioni, E. Bargagli, M. Di Tomassi, R. Pio, A. Pio, U. Maccari, C. Maggiorelli, M.G. Migliorini, L. Vignale, N. Pulerà, G.E. Carpagnano, M.P. Foschino Barbaro, A. Perrella, P.L. Paggiaro, Effects of omalizumab in severe asthmatics across ages: a real life Italian experience, *Respir. Med.* 119 (2016) 141–149.
- [10] T.S. Tat, A. Cilli, Evaluation of long-term safety and efficacy of omalizumab in elderly patients with uncontrolled allergic asthma, *Ann. Allergy Asthma Immunol.* 117 (2016) 546–549.
- [11] E.G. Tzortzaki, A. Georgiou, D. Kampas, M. Iemessios, M. Markatos, T. Adamidi, K. Samara, G. Skoula, A. Damianaki, S. Schiza, N. Tzakakis, N.M. Siafakas, Long-term omalizumab treatment in severe allergic asthma: the South-Eastern Mediterranean "real-life" experience, *Pulm. Pharmacol. Ther.* 25 (2012) 77–82.
- [12] M.H. Lefeuvre, J. Dean, J. Zhang, M.S. Duh, B. Gorsh, P. Lefeuvre, Impact of omalizumab on emergency-department visits, hospitalizations, and corticosteroid use among patients with uncontrolled asthma, *Ann. Allergy Asthma Immunol.* 109 (2012) 59–64.
- [13] I. Kuprys-Lipińska, P. Majak, J. Molinska, P. Kuna, Effectiveness of the Polish program for the treatment of severe allergic asthma with omalizumab: a single-center experience, *BMC Pulm. Med.* 16 (2016) 61.
- [14] G.J. Braunstahl, C.W. Chen, R. Maykut, P. Georgiou, G. Peachey, J. Bruce, The exPeRience registry: the "real-world" effectiveness of omalizumab in allergic asthma, *Respir. Med.* 107 (2013) 1141–1151.
- [15] C. Vennera Mdel, L. Pérez De Llano, S. Bardagí, P. Ausin, C. Sanjuas, H. González, J.A. Gullón, E. Martínez-Moragón, J.A. Carretero, E. Vera, J.F. Medina, F.J. Alvarez, L.M. Entrenas, A. Padilla, R. Irigaray, Picado C; Spanish Registry. Omalizumab therapy in severe asthma: experience from the Spanish registry—some new approaches, *J. Asthma* 49 (2012 May) 416–422.
- [16] M. Luu, M. Bardou, P. Bonniaud, F. Goirand, Pharmacokinetics, pharmacodynamics and clinical efficacy of omalizumab for the treatment of asthma, *Expert Opin. Drug Metab. Toxicol.* 12 (2016) 1503–1511.
- [17] I. Kuprys-Lipińska, P. Kuna, Loss of asthma control after cessation of omalizumab treatment: real life data, *Postepy Dermatol Alergol.* 31 (2014 Feb) 1–5.
- [18] R.G. Slavin, C. Ferioli, S.J. Tannenbaum, C. Martin, M. Blogg, P.J. Lowe, Asthma symptom re-emergence after omalizumab withdrawal correlates well with increasing IgE and decreasing pharmacokinetic concentrations, *J. Allergy Clin. Immunol.* 123 (2009) 107–113 e3.
- [19] M. Caminati, G. Senna, G. Stefanizzi, R. Bellamoli, S. Longhi, F. Chieco-Bianchi, G. Guarnieri, S. Tognella, M. Olivieri, C. Micheletto, G. Festi, E. Bertocco, M. Mazza, G. Rossi, A. Vianello, North East Omalizumab Network study group. Drop-out rate among patients treated with omalizumab for severe asthma: literature review and real-life experience, *BMC Pulm. Med.* 16 (2016) 128.
- [20] R.W. Dal Negro, S. Tognella, L.A. Pradelli, 36-month study on the cost/utility of add-on omalizumab in persistent difficult-to-treat atopic asthma in Italy, *J. Asthma* 49 (2012) 843–848.
- [21] C. Vennera Mdel, A. Valero, E. Uría, C. Forné, C. Picado, Cost-effectiveness analysis of omalizumab for the treatment of severe persistent asthma in real clinical practice in Spain, *Clin. Drug Investig.* 36 (2016) 567–578.
- [22] S. Maltby, P.G. Gibson, H. Powell, V.M. McDonald, Omalizumab treatment response in a population with severe allergic asthma and overlapping COPD, *Chest* 151 (1) (2017 Jan) 78–89.
- [23] G. Garcia, A. Magnan, R. Chiron, C. Contin-Bordes, P. Berger, C. Taillé, G. Devouassoux, F. de Blay, L.J. Couderc, A. Didier, D.S. O'Callaghan, P.O. Girodet, I. Bourdeix, V. Le Gros, M. Humbert, A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma, *Chest* 144 (2) (2013) 411–419.
- [24] J.J. López Tiro, E.A. Contreras, M.E. del Pozo, J. Gómez Vera, D. Larenas Linemann, Real life study of three years omalizumab in patients with difficult-to-control asthma, *Allergol. Immunopathol. (Madr)* 43 (2) (2015) 120–126.
- [25] G. Pelaia, L. Gallelli, P. Romeo, T. Renda, M.T. Busceti, A. Proietto, R.D. Grembiale, S.A. Marsico, R. Maselli, A. Vatrella, Omalizumab decreases exacerbation frequency, oral intake of corticosteroids and peripheral blood eosinophils in atopic patients with uncontrolled asthma, *Int. J. Clin. Pharmacol. Ther.* 49 (12) (2011) 713–721.
- [26] P.C. Almeida, E.V. Ponte, A. Souza-Machado, A.A. Cruz, Longitudinal trends in clinical characteristics and lung function of patients with severe asthma under treatment in Brazil, *BMC Pulm. Med.* 16 (1) (2016) 141.
- [27] C.A. Witt, A. Sheshadri, L. Carlstrom, J. Tarsi, J. Kozlowski, B. Wilson, D.S. Gierada, E. Hoffman, S.B. Fain, J. Cook-Granroth, G. Saiol, O. Sierra, T. Giri, M. O'Neill, J. Zheng, K.B. Schechtman, L.B. Bacharier, N. Jariour, W. Busse, M. Castro, NHLBI Severe Asthma Research Program (SARP). Longitudinal changes in airway remodeling and air trapping in severe asthma, *Acta Radiol.* 21 (8) (2014) 986–993.

- [28] M. Kupczyk, I. Kupriś, P. Górski, P. Kuna, Long-term deterioration of lung function in asthmatic outpatients, *Respiration* 71 (3) (2004) 233–240.
- [29] K. Matsunaga, T. Hirano, A. Oka, A. Tanaka, K. Kanai, T. Kikuchi, A. Havata, H. Akamatsu, K. Akamatsu, Y. Koh, M. Nakanishi, Y. Minakata, N. Yamamoto, Progression of irreversible airflow limitation in asthma: correlation with severe exacerbations, *J. Allergy Clin. Immunol. Pract.* 3 (5) (2015) 759–764.
- [30] T.R. Bai, J.M. Vonk, D.S. Postma, H.M. Boezen, Severe exacerbations predict excess lung function decline in asthma, *Eur. Respir. J.* 30 (3) (2007) 452–456.
- [31] M. Roth, J. Zhong, C. Zumkeller, C.T. S'ng, S. Goulet, M. Tamm, The role of IgE-receptors in IgE-dependent airway smooth muscle cell remodelling, *Plos One* 8 (2013) e56015.
- [32] M. Roth, F. Zhao, J. Zhong, D. Lardinois, M. Tamm, Serum IgE induced airway smooth muscle cell remodeling is independent of allergens and is prevented by omalizumab, *PLoS One* 10 (9) (2015) e0136549.
- [33] P. Mauri, A.M. Riccio, R. Rossi, D. Di Silvestre, L. Benazzi, L. De Ferrari, R.W. Dal Negro, S.T. Holgate, G.W. Canonica, Proteomics of bronchial biopsies: galectin-3 as a predictive biomarker of airway remodelling modulation in omalizumab-treated severe asthma patients, *Immunol. Lett.* 162 (2014) 2–10.
- [34] A.M. Riccio, R.W. Dal Negro, C. Micheletto, L. De Ferrari, C. Folli, A. Chiappori, G.W. Canonica, Omalizumab modulates bronchial reticular basement membrane thickness and eosinophil infiltration in severe persistent allergic asthma patients, *Int. J. Immunopathol. Pharmacol.* 25 (2012) 475–484.
- [35] M. Hoshino, J. Ohtawa, Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma, *Respiration* 83 (2012) 520–528.
- [36] T. Tajiri, A. Niimi, H. Matsumoto, I. Ito, T. Oguma, K. Otsuka, T. Takeda, H. Nakaji, H. Inoue, T. Iwata, T. Nagasaki, Y. Kanemitsu, Y. Izuhara, M. Mishima, Comprehensive efficacy of Omalizumab for severe refractory asthma: a time-series observational study, *Ann. Allergy Asthma Immunol.* 113 (2014) 470–475 e2.
- [37] L. Bjerner, The role of small airway disease in asthma, *Curr. Opin. Pulm. Med.* 201 (1) (2014) 23–30.