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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 Group[1]

[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

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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 (FEV_1, exacerbations, ACT, SABA use, asthma control levels, medications used e 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 FEV_1% 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 ([1]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).

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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 FEV_1 decline.

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 (FEV_1 <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 β2-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 (FEV_1, FVC, FEV_1/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 (FEV_1, 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 FEV_1, 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, FEV_1, 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 monosensitized 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. FEV_1% and FEV_1/FVC (evaluated on 125 patients) measured before Omalizumab treatment was similar in all 4 groups.

FEV_1% 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). FEV_1% values observed after >60 months were slightly lower (not