Evolution of uncontrolled severe asthma under Omalizumab and specialized care unit treatment.

Alberto Levy-Nahon[1-4], Lorena Piñel-Jiménez[1]*, Jesus Ramirez-Rodrigo[4], Lucia Prieto[4], Victoria Hidalgo-Sanjuan M[1] and Pedro Valdivielso[2-3]

[1]Pneumology Service, University Hospital 'Virgen de la Victoria', Málaga, Spain
[2]Internal Medicine Service, University Hospital 'Virgen de la Victoria' Málaga, Spain
[3]Department of Medicine and Dermatology, University of Málaga, Spain
[4]Department of Nursing, Faculty of Health Sciences, University of Granada (in Ceuta), Spain

Abstract

Severe uncontrolled asthma is a disabling and life-threatening disorder. This article evaluates the effectiveness of combining a specialized care clinic treatment with the prescription of Omalizumab (OML) when treating these patients. We analyzed 45 patients with severe uncontrolled asthma followed for 12 months, of which 30 had elevated levels of IgE and received omalizumab dose adjusted for weight and IgE levels. The overall effectiveness was measured through parameters such as emergency room visits (ER), the evolution of forced expiratory volume in one second (FEV1), the need for high-dose corticosteroids; Fractional exhaled nitric oxide (FENO) and a quality of life survey. At three, six and twelve months, all patients improved significantly in all measured parameters (p<0.05), except FENO, as a result of their treatment in the specialist office. The changes were even more favorable for patients who received OML in addition to the visits to the specialized care clinic, showing a significant interaction between drug use and clinical visit factors. Our results confirm that the benefits obtained in randomized clinical trials with OML and the specialist care of patients with severe asthma result in a significant clinical benefit in the context of everyday clinical practice.

Introduction

Bronchial asthma is one of the most frequent respiratory disorders, affecting 5% of the adult Spanish population [1], although its prevalence appears to be levelling off among adolescents [2]. The management of asthmatic patients is widespread among general practitioners, allergists and pneumologists, although the most severe forms prove challenging for professionals due to the associated disability, reduced quality of life and treatment costs.

The prevalence of severe uncontrolled asthma is not negligible; a recent study that recorded information from 164 hospital units in Spain over 6 months, showed that 666 (65.9%) patients among 36,649 adult asthmatics, met criteria for uncontrolled severe chronic asthma according to GINA criteria [3]. For this and other reasons, the creation of specific asthma units has led to improved assistance, a rational use of medical resources and the use of specific biologic therapies for this disease [4,5]. In this sense, the humanized monoclonal anti-IgE antibody Omalizumab (OML) is marketed in Europe since October 2005 and is indicated for the treatment of uncontrolled severe persistent asthma with high IgE levels. The use of OML in this type of patients has resulted in a reduced number of exacerbations while decreasing steroids use and improving the quality of life when compared to placebo (as shown in a recent systematic review of 6 randomized clinical trials [6]).

The aim of this study was to evaluate retrospectively the efficacy of an asthma specialist office in the clinical management of patients with uncontrolled severe persistent asthma and the potential benefit of treatment with OML.

Materials and Methods

We retrospectively analyzed medical records of patients with uncontrolled severe asthma treated between January 2008 and October 2009 at the Asthma office of the University Hospital "Virgen de la Victoria" in Malaga and selected those that met the following inclusion criteria: age over 14 years, clinical and functional diagnosis of uncontrolled severe persistent asthma [7] with more than 1 year follow-up and having completed at least the follow-up visits at 3, 6 and 12 months. We excluded smokers or patients with >1 year smoking history, pregnancy, comorbidities such as intercurrent infections or active neoplasia, and the presence of chronic obstructive pulmonary disease (COPD) or overlap syndrome according to GOLD criteria [8].

At the first visit, information on age, sex, anthropometric parameters, smoking habits, comorbidities, other clinical forms of atopy, and medications in used were collected, as well as a chest X-ray and an ECG. Additionally, a blood sample was performed for measuring blood count and total serum IgE by radioallergosorbent test (RAST). Moreover, during the first and subsequent visits (3, 6 and 12 months), data was collected on percentage of predicted forced expiratory volume in 1 second (FEV1 %), the number of visits to the emergency room (ER)

in the previous three months, the inflammatory activity of the airways estimated as fractional expiratory nitric oxide (FENO), the anti-inflammatory treatment needs and a test of quality of life. Spirometry was performed with a portable spirometer (ESPIROBANK 2, Medical International Research, Waukerna, WI, USA), following the recommendations for this purpose by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and using the recognized normal range for the Spanish population [9]. The FENO was measured by chemiluminescence, using a portable device (MIOX-MIN, Aerocrine, Solna, Sweden). For the quality of life survey we used the Mini asthma Quality of Life Questionnaire (mQLQ) [10], generously made available by Dr. E. Juniper. We defined as "clinically important difference" the minimum score difference that the patient perceives as decisive and which, in the absence of side effects and / or exacerbation, would justify a change in the clinical management of the patient. A change of 0.5 in total questionnaire score is equivalent to a "clinically important change." Differences of 1.0 represent a moderate change and >1.5 represent large changes [11].

The anti-inflammatory treatment needs were analyzed by assigning the following scores: 1=inhaled corticosteroids (ICS) at medium doses; 2=high-dose ICS; 3=long-acting β2-receptor agonists (LABAs) plus medium-dose ICS; 4=LABAs + high-dose ICS; and 5=LABAs + high-dose ICS + oral corticosteroids. Patients were treated following the recommendations of the GINA 2015; thus, patients with total IgE levels >100 IU were treated with OML, administered subcutaneously at a dose adjusted for weight and IgE levels, as indicated [12]. Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc, Michigan, USA). Variables are shown as mean ± SD or as a percentage (%). For each group, the variation along the follow-up period was estimated by repeating the analysis of variance. Significant differences between groups at each visit

and interaction between the 'visit' and the 'OML' factor variables were tested using respectively the Mann-Whitney test and the Friedman test.

As this is a retrospective analysis of clinical practice and the data was anonymized once recorded, informed consent was not required. The study received approval from the ethics committee of the center.

Results

Of 225 patients medical records reviewed, 180 were excluded from further analysis according to the previous determined criteria: 90 had less than 12 months of follow-up, 37 changes the asthma level at visit 2, 33 were lost during the follow-up and 20 because of treatment discontinuation. The final group therefore consists of 45 patients, of whom 30 had been treated with Omalizumab due to basal levels of total IgE >100 IU. Only 5 patients treated with OML were rejected from the analysis; 3 due to treatment non adherence and 2 as a result of adverse effects (diarrhea in one case and alopecia in one case) (Figure 1).

Patient baseline characteristics are shown in (Table 1), which highlights that at baseline the only difference between the groups was total IgE levels. (Table 2) shows the changes in FEV1, quality of life, FENO, anti-inflammatory treatment needs and number of visits to the ER in both groups during the follow-up. There was a statistically significant improvement ($p<0.05$) in both groups in all variables except the FENO. About the number of visits to the ER, both groups improved significantly, without differences between them (from 4.6 ± 4.5 in OML group and 3 ± 1.9 in control group to 0.2 after 12 months of follow-up). On the contrary, improvement in FEV1% and quality of life questionnaire was greater in the group receiving OML than in the control group, although it is noteworthy that there was a significant interaction between the variables "treatment
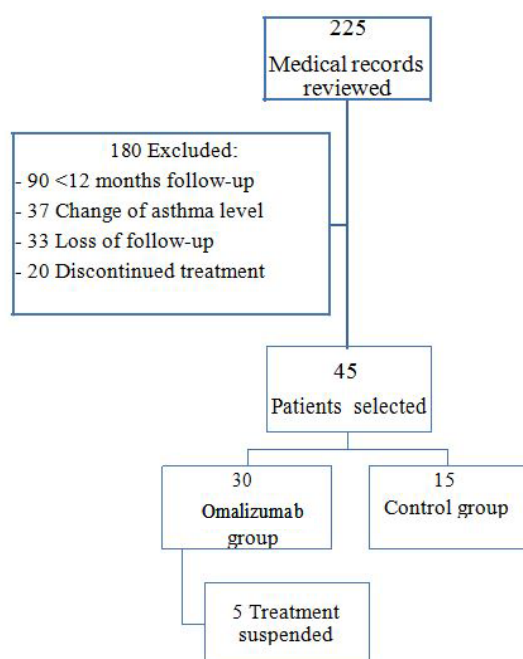

Figure 1. Flow diagram of patients who met inclusion/exclusion criteria.

group" and "specialized office effect". When we categorized the changes in quality of life from 1 (change <0.5) to 4 (change >1.5), we observed that the group treated with OML had a higher percentage of patients in category 4 than the control group (Figure 2).

Discussion

Although most asthma patients receive treatment, a considerable proportion of them are only partially or poorly controlled [13]. The National Asthma Education and Prevention Program

Table 1. *Characteristics of the patients at base-line visit.*

Variables	Total	Omalizumab group	Control group	Statistical significance
	N = 45	N = 30	N = 15	
Male sex No (%)	31-68.9	22-71	9 (60)	
Age (years)	54±14	55±12	54±17	NS
BMI (Kg/m²) mean ± SD	31±7	31±7	32±8	NS
Asthma evolution (years) mean ± SD	25±17	26±19	23±14	NS
Total IgE (IU) mean ± SD	269 ± 274	378 ± 276	50±32	<0.05
Clinical forms of Atopy No (%)				
- Rhinitis	- 26 (57.8)	- 18 (69.2)	- 8 (30.8)	
- Conjunctivitis	- 32 (71.1)	- 18 (56.3)	- 14 (43.7)	
- Dermatitis	- 1 (2.2)	- 1 (100)	- 0	
BMI: Body Mass Index; NS: No Statistically Significant; IU: International Unit; SD: Standard Deviation				

Table 2. *Parameters changes according to treatment group and follow-up time.*

		Baseline Mean ±SD	3 Months Mean ±SD	6 Months Mean ±SD	12 Months Mean ±SD	Analysis of variance for repeated measurements
FEV1 (%)[d]	OML	54 ± 10	66± 17[a]	72 ± 16[a b]	75 ± 16[a b c]	<0.05
	CONT	53± 9	62± 17[a]	64 ± 14[a]	64 ± 13[a]	<0.05
FENO (PPM)	OML	40 ± 32	35 ± 33	30 ± 22	30 ± 22	NS
	CONT	35 ± 43	29 ± 22	28 ± 20	27 ± 19	NS
Emergency room visits	OML	4.6 ± 4.5	1.0 ± 1.9[a]	0.2 ± 0.5[a b]	0.2 ± 0.4[a b]	<0.05
	CONT	3.0 ± 1.9	1.0 ± 1.2[a]	0.5 ± 1.1[a]	0.2 ± 0.6[a b]	<0.05
mQLQ[d]	OML	29 ± 8	38 ± 12[a]	50 ± 15[a b]	57 ±14[a b c]	<0.05
	CONT	26 ± 7	33 ± 14[a]	34 ± 15[a]	39 ± 14[a b]	<0.05
Anti-inflammatory treatment needs	OML	4.4 ± 1.4	4 ± 1.5	4 ± 1.5[a]	4 ± 1.4[a b]	<0.05
	CONT	4.9 ±1.9	4.7 ± 1.8	4.1 ± 1.5[a]	4 ± 1.4[a b]	<0.05

Sig: Statistical Significance; NS: No Statistically Significant; SD: Standard Deviation
a = p<0.05 compared to the baseline; b = p<0.05 compared to 3 months; c = p<0.05 compared con 6 months d = p<0.05 The interaction between the effects of follow-up and treatment group.
FEV1: Forced Expiratory Volume in one second; FENO: Fractional Exhaled Nitric Oxide; PPM: Parts Per Million; mQIQ: Mini Asthma Quality of Life Questionnaire
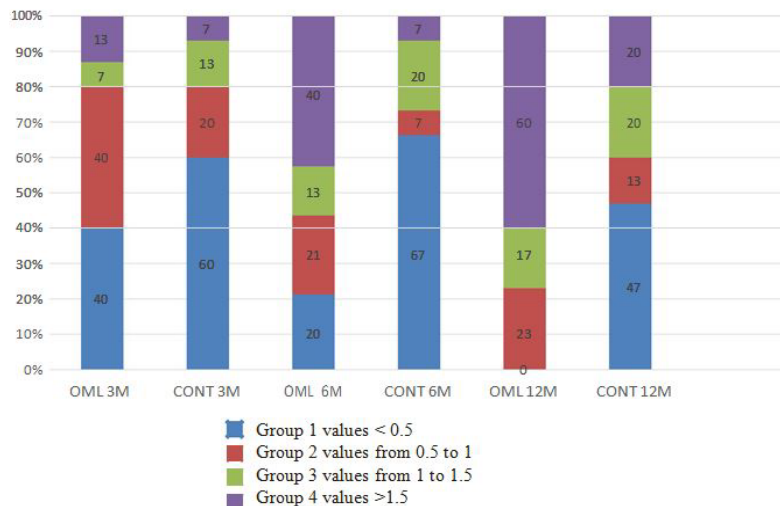

Figure 2. *mQLQ changes as a consequence of follow-up and type of treatment.*

(NAEPP) recommends that patients who are receiving medium-dose ICS + LABA (i.e., step 4 of care or higher) require a consultation with an asthma specialist [14,15]. However, only 22% of asthma patients in the U.S. are treated by pneumonologists or allergists [16]. In Spain, 71% of patients with asthma treated by primary care physicians and 55% of patients treated at pneumonology and allergy specialist clinics, are poorly controlled [17,18]. In this context, our study shows that severe persistent asthma patients clearly benefit from inclusion in a specialized third-level asthma office. Thus, the control group, which did not receive biological therapy, reduced with statistical significance the number of ER visits as well as the need for anti-inflammatory medication. This was coupled with the also significant improvement of the FEV1% and the quality of life, assessed at the 6 and 12 months follow-up. The reasons behind why visiting a specialist is more beneficial than applying the usual care are related to better implementation of international guidelines, a reduction of the variance in clinical practice and application of techniques for disease control and cutting-edge treatments [5], as well as better patient treatment adherence [19].

As expected, patients with IgE-mediated asthma who received OML showed a marked improvement in FEV1%, number of emergency room visits, quality of life and number of anti-inflammatory treatments. We want to emphasize that in the case of the FEV1% and the quality of life mini-survey, the improvement at 6 and 12 months was even greater in the control group which did not receive biological treatment. None of this is a surprise; some randomized clinical trials [20,21] have shown how the personalized follow-up of patients with uncontrolled persistent asthma leads to an improvement of their evolution [22,23], as was the case of our patients. The design of this study, to assess the monitoring of patients with and without biological treatment, allows us to highlight the relevance of the interaction between the follow-up in a specialist office and OML treatment. The main limitations of this study are its retrospective nature and small sample size due to it being limited to a single hospital and to the use of a number of exclusion criteria. We do not analyze the evolution of those two subjects who, although being eligible for OML treatment, did not tolerate it. In summary, our study confirms that the establishment of monographic asthma offices and Omalizumab treatment in selected patients are beneficial for patients with persistent uncontrolled asthma.

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*Correspondence to:
Lorena Piñel Jiménez
Pneumology Service
University Hospital 'Virgen de la Victoria'
Málaga, Spain.
Tel: +34622200763
E-mail: lorenapinel@gmail.com