

PHARMACOTHERAPY

Effects of Omalizumab in Non-Atopic Asthma: Results from a Spanish Multicenter Registry

LUIS PÉREZ DE LLANO, M.D., PH.D.,¹ MARÍA DEL CARMEN VENNERA, M.D.,^{2,3,4} FRANCISCO J. ÁLVAREZ, M.D.,⁵ JUAN F. MEDINA, M.D.,⁵ LUIS BORDERÍAS, M.D., PH.D.,⁶ CONCHA PELLICER, M.D.,⁷ HÉCTOR GONZÁLEZ, M.D., PH.D.,⁸ JOSÉ A. GULLÓN, M.D., PH.D.,⁸ EVA MARTÍNEZ-MORAGÓN, M.D., PH.D.,⁹ CARLOS SABADELL, M.D.,¹⁰ SOLEDAD ZAMARRO, M.D.,¹¹ AND CÉSAR PICADO, M.D., PH.D.^{2,3,4}; on behalf of the Spanish Registry

¹Department of Pneumology, Hospital Xeral-Calde, Rua Doutor Ochoa, Lugo, Spain.

²Department of Pneumology and Respiratory Allergy, Hospital Clínic, Universitat de Barcelona, Spain.

³Centro de Investigaciones Biomedicas en Red de Enfermedades Respiratorias (CIBERES), Palma de Mallorca, Spain.

⁴Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

⁵Department of Pneumology, Hospital Universitario V. del Rocío, Sevilla, Spain.

⁶Department of Pneumology, Hospital San Jorge, Huesca, Spain.

⁷Department of Pneumology, Hospital Francesc de Borja, Gandía, Valencia, Spain.

⁸Department of Pneumology, Hospital Universitario de Canarias, San Cristobal de la Laguna, Tenerife, Spain.

⁹Department of Pneumology, Hospital de Sagunto, Sagunto, Valencia, Spain.

¹⁰Department of Pneumology, Hospital de Figueras, Girona, Spain.

¹¹Department of Allergy, Hospital Rafael Méndez, Lorca, Murcia, Spain.

Aim. To evaluate the effectiveness of omalizumab in non-atopic asthma. **Methods.** Using data from a multicenter registry of severe asthma, we evaluated and compared the clinical outcome of 29 omalizumab-treated severe non-atopic asthmatics with 266 omalizumab-treated severe allergic asthmatics. Effectiveness was assessed by considering severe exacerbations, pulmonary function, the Global Evaluation of Treatment Effectiveness (GETE) scale, and Asthma Control Test (ACT). **Results.** Omalizumab demonstrated significant improvement in the clinical status of non-atopic asthmatics as measured by GETE, which rose from 1.6 ± 1.1 to 2.8 ± 0.8 at 4 months ($p = .0215$) to 2.9 ± 0.9 at 1 year ($p = .0093$) and to 3.4 ± 0.6 at 2 years ($p = .0078$), and by the ACT, which increased from 13.0 ± 5.5 to 17.5 ± 5.4 at 4 months ($p = .0236$) to 17.9 ± 4.8 at 1 year ($p = .0136$) and to 20.6 ± 3.9 at 2 years ($p = .0024$). Forced expiratory volume in 1 second (FEV₁) improved from $61.0 \pm 19.4\%$ to 65.1 ± 17.2 at 4 months to 64.1 ± 24.7 at 1 year and to 67.3 ± 23.0 at 2 years, but without significant differences between initial and follow-up measurements ($p = .52$, $.91$, and $.45$, respectively) and exacerbations decreased from 3.1 ± 3.5 to 1.9 ± 2.8 at 1 year ($p = .1709$) to 1.8 ± 4.4 at 2 years ($p = .2344$). The results were not significantly different from those obtained in atopic asthmatics. **Conclusion.** Anti-IgE therapy can be effective in non-atopic severe asthma.

Keywords efficacy, IgE-mediated diseases, non-allergic patients, omalizumab, uncontrolled severe asthma

INTRODUCTION

Although asthma can generally be controlled with inhaled corticosteroids (ICSs) and long-acting β_2 -agonists (LABAs), severe persistent asthma often responds poorly to both inhaled and oral corticosteroids (1) and requires progressively increasing doses to maintain stability. It has been estimated that around 10% of asthma patients may be classified as severe on the basis of the consensus definition embracing persistent symptoms, airflow limitation, and resistance to treatment (2,3). Moreover, about one-third of adult patients with asthma are classified as non-atopic or non-allergic, based on the absence of circulating IgE directed against local aeroallergens detected by skin prick test (SPT) or in vitro techniques (RAST or ELISA).

Non-atopic asthmatics tend to have more severe disease, often associated with chronic rhinosinusitis (CRS) and nasal polyposis (NP), but apart from the absence of reactivity to aeroallergens, their clinical course is similar to that of atopic patients (4). The percentage of asthmatics with severe disease and a negative SPT varies from 50% in the ENFUMOSA cross-sectional study (1) to 17–34% in the SARP study (5).

Omalizumab (Xolair®, Novartis Europharm Limited, Horsham, West Sussex, United Kingdom), a humanized monoclonal anti-IgE antibody that targets the interaction between IgE molecules and IgE receptors, has demonstrated its efficacy in severe IgE-mediated allergic asthma, both in clinical studies and in the post-marketing experience (6–11). In fact, we have previously reported that omalizumab is an effective therapy in the severe allergic asthma population included in the Spanish registry (11). Nowadays, omalizumab is indicated in Europe as an add-on therapy aimed at

*Corresponding author: María del Carmen Vennera, M.D., Department of Pneumology and Respiratory Allergy, Hospital Clínic, Villarroel 170, Barcelona 08036, Spain, USA. Tel: +34 932 275 540; Fax: +34 932 275 455; E-mail: cvennera@clinic.ub.es

improving asthma control in patients (6 years and above) with severe persistent allergic asthma that remains uncontrolled despite daily high-dose inhaled corticosteroids plus a long-acting inhaled beta2-agonist. However, it is yet to be clarified whether omalizumab has a role to play in non-allergic asthmatics.

The purpose of the present study is to analyze data from the Spanish registry of severe asthma in order to evaluate the effectiveness of omalizumab in a population of 29 severe non-atopic asthmatics and to compare it with a control group of 266 allergic asthmatics who received the same treatment.

PATIENTS AND MATERIAL AND METHODS

Study Design and Patients

Patients were recruited from an ongoing observational registry involving 30 certified centers from all over Spain. Specialists in Allergology and Pneumology were offered the opportunity to participate in the study. The registry was designed to gather data on the clinical characteristics, treatment patterns, and outcome in consecutive adult patients with severe asthma. Asthma was left to the chest physician judgment according to his/her routine clinical practice. All omalizumab-treated asthmatics were included in the present analysis. Patients were managed on the basis of the clinical practice of the physicians corresponding to the participating hospital centers. Omalizumab was prescribed only in severe cases: steps 5 and 6 of the Spanish Guidelines on the Management of Asthma (GEMA) (12) and step 5 of the Global Initiative for Asthma international guidelines (GINA) (13). The drug was prescribed on-label in asthmatics with specific IgE against common inhalant allergens and off-label (for "compassionate use," as defined by Spanish legislation) in those with negative results with SPT, RAST, and ELISA.

This study was conducted according to Good Clinical Practice (GCP) standards and the Helsinki Declaration, and it was approved by the Ethics Committee of the Clinic Hospital of Barcelona. All patients provided written informed consent to their participation in the study. All the visits were integrated into routine practice for assessing the evolution of severe asthma patients.

Methods

The data were recorded in each hospital on a computer-based case report form. These reports were then submitted via a secure website (www.bancodatosasma.com) to a centralized coordinating center (Clinic Hospital, University of Barcelona) responsible for all data management. The patients' identities remained confidential, each patient being identified solely by a single number assigned by the study's coordinating center.

Baseline data regarding the 12-month period prior to omalizumab treatment were collected: age; sex; body mass index (BMI); clinical characteristics of asthma (time since diagnosis, total IgE level, allergic status documented by SPT and/or

specific IgE for common aeroallergens including house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), moulds (*Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, and *Penicillium notatum*), pollens (grass mix, *Parietaria judaica*, *Artemisia vulgaris*, *Olea europaea*, *Platanus acerifolia*, *Cupressus arizonica*), and dog and cat dander. Previous asthma exacerbations; FEV₁ (% of predicted), coexisting conditions such as intolerance to non-steroidal anti-inflammatory drugs (NSAIDs), CRS, NP, Asthma Control Test (ACT) (14), and asthma-related medication were also recorded. Patients were evaluated 4 months after beginning treatment with omalizumab in order to assess the therapy's effectiveness and safety, and after every 12 and 24 months of the treatment period thereafter. Any changes in the concomitant medications during the follow-up, the omalizumab dosage or the dosing schedule was recorded. Omalizumab-related adverse effects and causes of discontinuation were also registered.

The effectiveness of omalizumab over the treatment period was evaluated via the reduction in severe exacerbations and improvements in pulmonary function and clinical tests. Severe exacerbations were defined as deterioration in asthma resulting in hospitalization or emergency room treatment, or the need for oral steroids for ≥ 3 days (as considered appropriate by the investigator). The clinical efficacy was assessed based upon the responses to the Spanish version of the ACT questionnaire (14) and to the Global Evaluation of Treatment Effectiveness (GETE) scale (15). The ACT is reliable, valid, and responsive to changes in asthma control over time. A cut-off score of ≤ 19 identifies patients with poorly controlled asthma (14). The GETE five-point scale requires a treating physician to judge whether the patient's overall response to treatment is excellent, good, moderate, or poor, or whether his or her condition is worsening. A GETE rating of "good" or "excellent" defined a patient as a "responder" (16) and only these patients continued with omalizumab therapy. Well-controlled asthma was defined as no exacerbations and an ACT score > 19 .

Statistical Analysis

The categorical variables were described as absolute and relative frequencies, while continuous variables were reported as the mean and standard deviation or medians and quartiles, including the total number of valid values. In order to avoid losing data due to missing data, we used the pairwise missing data deletion method (visit-wise method). Comparison of the quantitative variables was based on the use of non-parametric tests (Wilcoxon test). The chi-squared test and McNemar test were used to compare the categorical variables. Mann-Whitney *U*-test was used for comparison of changes in clinical (GETE; ACT, exacerbations) and functional (FEV₁) parameters between the two groups (allergic and non-allergic). All calculations were made using the SAS version 9.2 statistical package (SAS Institute INC, Cary, NC,

USA), applying two-tailed tests, with a level of significance of .05.

RESULTS

This study included a total of 295 severe omalizumab-treated asthmatic patients (266 allergic and 29 non-allergic). The clinical and functional outcomes of the 266 atopic severe asthmatics has previously been reported (11). Asthma had been diagnosed 27.8 ± 13.8 years before the introduction of anti-IgE therapy. The mean follow-up time after omalizumab initiation was 27.1 ± 12.3 months for the negative prick test group and 26.8 ± 13.7 months for the positive prick test group ($p > .05$). All patients attended at least the first follow-up visit at 4 months, while 27/29 non-atopic patients attended the 1-year visit and 14 of them attended the 2-year visit.

The demographic and clinical characteristics are compared in Table 1. Briefly, non-atopic asthmatics were older (59.6 ± 10.6 vs. 51.0 ± 13.7 ; $p = .0011$), they were more frequently diagnosed with nasal polyps (48.8% vs. 25.2%; $p = .0239$) and hypersensitivity to aspirin/NSAIDs (36% vs. 18.9%; $p = .0431$), their IgE levels were significantly lower (251.8 ± 355.9 vs. 412.6 ± 546.5 ; $p = .0172$), and they were treated more often with systemic corticosteroids (55.2% vs. 33.5%; $p = .0204$).

Omalizumab was discontinued in 18% of the allergic patients and in 17.2% of the non-atopic subgroup. Regarding tolerance, 6.9% of non-atopic patients experienced some adverse effect (cephalea being the most frequent).

The performance evaluated by the GETE increased from 1.6 ± 1.1 to 2.8 ± 0.9 at 4 months ($p = .0215$) to 2.9 ± 0.9 at 1 year ($p < .0093$) and 3.4 ± 0.6 at 2 years ($p = .078$) in the non-atopic group. Furthermore, the ACT increased from 13.3 ± 5.5 to 17.5 ± 5.4 at 4 months ($p < .0236$) to

17.9 ± 4.8 at 1 year ($p = .0136$) and 20.6 ± 3.9 at 2 years ($p = .0024$). Clinical improvement was not significantly different between the atopic and non-atopic groups. FEV₁ improved from $61.0 \pm 19.4\%$ to 65.1 ± 17.2 at 4 months to 64.1 ± 24.7 at 1 year and 67.3 ± 23.0 at 2 years, but without significant differences between them ($p = .52$, .91, and .45, respectively). Severe exacerbations decreased non-significantly in the non-atopic group [from 3.1 ± 3.5 to 1.9 ± 2.8 at 1 year ($p = .1709$) and 1.8 ± 4.4 at 2 years ($p = .2344$)], but the magnitude of the effect was similar in both groups at 1 year and 2 years ($p = .18$ and $p = .17$). Well-controlled asthma – defined as no exacerbations and an ACT score > 19 – was achieved in 17% of non-atopic patients at 1 year versus 29.3% in atopic asthmatics ($p = .159$). These results are summarized in Figure 1.

DISCUSSION

Only three case reports to date have addressed the effectiveness of omalizumab in patients with severe non-allergic asthma (17–19). In our series, the drug demonstrated a beneficial effect in a group of 29 patients with these characteristics. Omalizumab is only indicated for patients with allergic asthma; however, the lack of therapeutic alternatives for non-atopic severe asthma led many physicians to prescribe it off-label, for “compassionate use.” Over the course of the study, the GETE scale and ACT score increased significantly. Furthermore, we observed a non-significant increase in pulmonary function values and a decrease in severe asthma exacerbations, but not statistically different from that achieved in atopic asthmatics. All in all, the global results are almost similar to those obtained in atopic patients (6–11).

It has been demonstrated that both atopic and non-atopic asthmatics manifest similar immunologic profiles that promote IgE switching such as increased IL-4 and IL13 and expression of FcεRI mRNA (20–23). Moreover, another study showed that bronchial mucosal IgE synthesis is a feature of atopic as well as non-atopic asthma, – further evidence that both types of asthma are quite similar in terms of their cellular and molecular immunopathology (24). Therefore, even in the absence of a proven aeroallergen, IgE might have decisive effects on the asthmatic inflammatory response, leading to both bronchial hyper-reactivity and remodeling. It is also well known that omalizumab binds to antigen-specific and non-specific IgE; this characteristic provides scientific support for anti-IgE therapy in non-atopic patients (25).

Prevalence of CRS with NP and aspirin hypersensitivity was very high in our patients. These observations concur with previous studies reporting the frequent association of moderate/severe persistent asthma with both aspirin hypersensitivity and CRS and nasal polyps (26–28). Moreover, aspirin-intolerant asthma has been associated with increased airway remodeling (28).

This study has several limitations. The results were obtained from a large and prospective registry of patients with severe asthma. Participation in the registry was offered to all Spanish pulmonary and allergy specialists, but it is

TABLE 1.—Clinical and demographic characteristics.

Severe asthma patients	Prick + <i>n</i> = 266	Prick – <i>n</i> = 29	<i>p</i> -Value
Gender			
Male	31.2%	27.6%	.688
Female	68.8%	72.4%	
Age (years)	51.0 (13.7)	59.6 (10.6)	.0011
BMI	28.2 (5.6)	28.6 (5.5)	.8227
CRS (with and without NP)	60%	51.7%	.3893
NP	25.2%	44.8%	.0239
NSAIDs intolerance	18.9%	36%	.0431
CSCs	33.5%	55.2%	.0204
Years since asthma diagnosis	28.3 (14.8)	23.4 (13.4)	.1123
Total basal IgE (IU/ml)	412.6 (546.5)	251.8 (355.9)	.0172
Basal ACT	14.4 (4.6)	13.0 (5.5)	.1369
Severe exacerbations (average of annual number)	3.6 (3.6)	3.1 (3.5)	.0545
FEV ₁ (% of predicted)	63.8 (21.2)	61.0 (19.4)	.5359
Omalizumab dose (mg/month)	414.7 (206.7)	351.7 (176.0)	.1379
Time of follow-up (months)	26.8 (13.7)	27.1 (12.3)	.9070

Notes: Results are expressed as mean with standard deviation in brackets or as a percentage. BMI, body mass index; CRS, chronic rhinosinusitis; NP, nasal polyposis; NSAID, non-steroidal anti-inflammatory drug; CSC, continuous systemic corticosteroid; IgE, immunoglobulin E; ACT, Asthma Control Test; FEV₁, forced expiratory volume in 1 second.

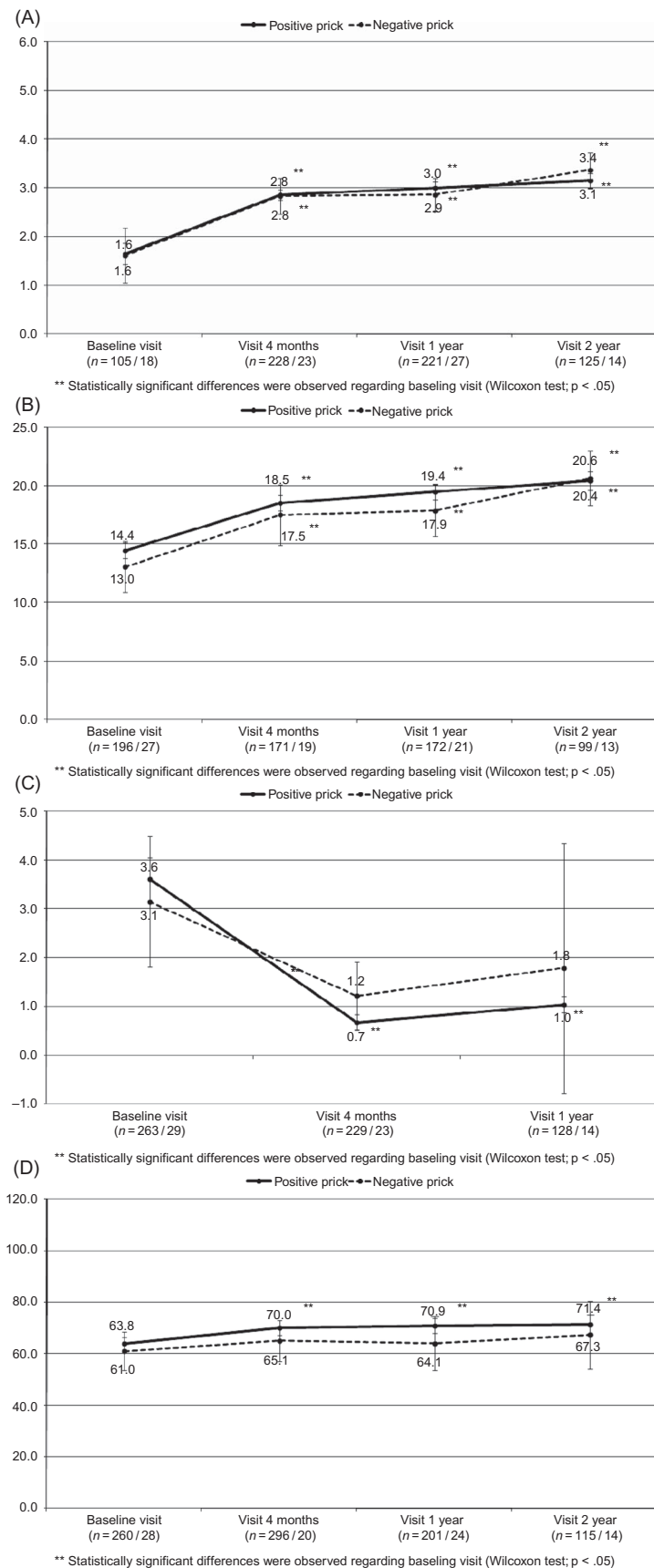


FIGURE 1.—The efficacy of omalizumab in severe asthma. Comparison between atopic and non-atopic patients. (A) Evolution of GETE. Physician-rated GETE: score 3 (good) and score 4 (excellent) correspond to responder-patients. Means are shown in the chart. Note: GETE, global evaluation of treatment effectiveness. (B) ACT evolution. Means are shown in the chart. Notes: ACT, Asthma Control Test. (C) Average of exacerbations during the previous year and observational period. Confidence intervals (95%) for means are shown in the chart with vertical black line segments. (D) Pulmonary function (assessed by FEV₁) during follow-up. Means are shown in the chart. Note: FEV₁, forced expiratory volume in 1 second.

possible that the patient population included in this study was not generalizable to the Spanish health care system. The registry describes the “real world” of patients with severe asthma, managed according to the current guidelines (all the patients received a high dose of inhaled ICS/LABA in combination and many of them also received concomitant oral corticosteroids). One limitation of our study is that the diagnosis of asthma was based solely on the judgment of the chest physician caring for the patient. In contrast to the rigorously controlled conditions of randomized clinical trials, this study cannot exclude a placebo effect and it required retrospective comparison, because effectiveness during treatment was compared to that of the previous year. It must be pointed out that the placebo effect in asthma is quite strong, particularly with respect to patient-centered outcomes (29). In fact, a recently published study showed that omalizumab consistently improved asthma control, but this improvement was not significant when compared with the placebo control group (30). However, it should be noted that we have also found clinically relevant improvements in objective parameters such as exacerbations and lung function.

It has to be considered that only 14 of the 29 non-allergic asthmatics attended the 2-year visit, but omalizumab was discontinued only in five cases due to absence of a measurable response; the rest of the patients were followed up for 2 years. This fact could lead to the over-estimation of the long-term clinical effect of the drug, as assessed by clinical and functional parameters that were performed only in those asthmatics who continued the treatment. Nevertheless, this concern could be applied equally to the group of allergic subjects and, as previously stated, no significant differences were found between the responses to omalizumab of the two groups.

Another limitation stems from the assumption that the absence of demonstrable specific IgE antibodies and/or positive SPT results means that an asthmatic can be confidently classified as non-atopic. In fact, as the range of potential allergenic agents is considerably larger than the current diagnostic tests can address, the possibility of a false-negative result is likely (31). Moreover, atopy is an age-related phenomenon that decreases over time (32). It is therefore possible that those subjects with non-atopic asthma may previously have been atopic, as the non-atopic subjects with asthma in our study were significantly older. However, the SPT offers the best positive predictive value and is the method most widely used in clinical practice to diagnose allergy. Furthermore, our population showed clinical findings typical of non-allergic asthma (lower IgE levels, more frequent diagnosis of nasal polyps and hypersensitivity to NSAIDs).

In conclusion, this study shows that anti-IgE therapy can be an effective modality for treating non-atopic severe asthma. Further studies with an adequate methodology are needed to definitely establish the role of omalizumab in this setting.

ACKNOWLEDGMENTS

Dr Vennera, Dr Picado, and Dr Bardagí contributed to the study design. Dr Pérez de Llano, Dr Vennera, and Dr Picado contributed to the results interpretation and

manuscript. All authors have recruited the patients. Dr Pérez de Llano is the guarantor of the entire manuscript. Gerard Traveria from Adkoma Health Research performed the statistical analysis. Dr Ramón Mora from Novartis has supplied all kind of scientific information. Marc Castellví from NICASE (www.bancodatosasma.com) was our Software Product Manager.

DECLARATION OF INTEREST

Cesar Picado: In the last 5 years, C. Picado has been awarded grants for Research Projects from Uriach SA, Phadia, Chiesi, AstraZeneca, Leti, Novartis, and MSD; and he has participated as investigator in Clinical Trials for Uriach SA and Chiesi. Dr Pérez de Llano L, Dr Vennera M, and Dr Borderías L have received payments from Novartis Farmacéutica for lectures and consultancies and support for attendance of scientific meetings. The rest of the authors declare that they have no competing interests.

REFERENCES

1. European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA). The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Respir J* 2003; 22(3):470–7.
2. Wenzel SE, Busse WW. National heart, lung, and blood institute's severe asthma research program. Severe asthma: lessons from the severe asthma research program. *J Allergy Clin Immunol* 2007; 119(1):14–21.
3. Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, Calhoun WJ, Castro M, Chung KF, Clark MP, Dweik RA, Fitzpatrick AM, Gaston B, Hew M, Hussain I, Jarjour NN, Israel E, Levy BD, Murphy JR, Peters SP, Teague WG, Meyers DA, Busse WW, Wenzel SE. National heart, lung, blood institute's severe asthma research program. Characterization of the severe asthma phenotype by the national heart, lung, and blood institute's severe asthma research program. *J Allergy Clin Immunol* 2007; 119(2):405–413.
4. Miller MK, Johnson C, Miller DP, Deniz Y, Bleecker ER, Wenzel SE. Severity assessment in asthma: An evolving concept. *J Allergy Clin Immunol* 2005; 116:990–S.
5. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino RJ, Castro M, Curran-Everett D, Fitzpatrick AM, Gaston B, Jarjour NN, Sorkness R, Calhoun WJ, Chung KF, Comhair SA, Dweik RA, Israel E, Peters SP, Busse WW, Erzurum SC, Bleecker ER. National heart, lung, and blood institute's severe asthma research program. Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med* 2010; 181(4):315–323.
6. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, Beeh KM, Ramos S, Canonica GW, Hedgecock S, Fox H, Blogg M, Surrey K. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005; 60(3):309–316.
7. Molimard M, de Blay F, Didier A, Le Gros V. Effectiveness of omalizumab (Xolair) in the first patients treated in real-life practice in France. *Respir Med* 2008; 102(1):71.
8. Brusselle G, Michils A, Louis R, Dupont L, Van de Maele B, Delobbe A, Pilette C, Lee CS, Gurdain S, Vancayzeele S, Lecomte P, Hermans C, MacDonald K, Song M, Abraham I. “Real-life” effectiveness of omalizumab in patients with severe persistent allergic asthma: The PERSIST study. *Respir Med* 2009; 103(11):1633–1642.
9. Korn S, Thielen A, Seyfried S, Taube C, Kornmann O, Buhl R. Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany. *Respir Med* 2009; 103(11):1725–1731.
10. Cazzola M, Camiciottoli G, Bonavia M, Gulotta C, Ravazzi A, Alessandrini A, Caiuffa MF, Berra A, Schino P, Di Napoli PL, Maselli R, Pelaia G, Bucchioni E, Paggiaro PL, Macchia L. Italian real-life experience of omalizumab. *Respir Med* 2010; 104(10):1410–1416.

11. Vennera MD, Pérez De Llano L, Bardagí S, Ausin P, Sanjuas C, González H, Gullón JA, Martínez-Moragón E, Carretero JA, Vera E, Medina JF, Alvarez FJ, Entrenas LM, Padilla A, Irigaray R, Picado C; on behalf of the Spanish Registry. Omalizumab Therapy in Severe Asthma: Experience from the Spanish Registry-Some New Approaches. *J Asthma* 2012; 49(4):416–22.
12. GEMA. 2009. Guía Española para el manejo del asma. Editorial Luzan 5. Madrid. Available at: www.gemasma.com. Accessed March 20, 2012.
13. GINA. 2006. Global Initiative for Asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report updated December 2011. Available at: <http://www.ginasthma.com>. Accessed March 20, 2012.
14. Vega JM, Badia X, Badiola C, López-Viña A, Olaguibel JM, Picado C, Sastre J, Dal-Ré R; Covalair Investigator Group. Validation of the Spanish version of the Asthma Control Test (ACT). *J Asthma* 2007; 44(10):867–72.
15. Holgate S, Buhl R, Bousquet J, Smith N, Panahloo Z, Jimenez P. The use of omalizumab in the treatment of severe allergic asthma: A clinical experience update. *Respir Med*. 2009; 103(8):1098–113.
16. Bousquet J, Siergiejko Z, Swiebocka E, Humbert M, Rabe KF, Smith N, Leo J, Peckitt C, Maykut R, Peachey G. Persistence of response to omalizumab therapy in severe allergic (IgE-mediated) asthma. *Allergy*. 2011; 66(5): 671–8.
17. Van den Berge M, Pauw RG, de Monchy JG, van Minnen CA, Postma DS, Kerstjens HA. Beneficial effects of treatment with anti-IgE antibodies (Omalizumab) in a patient with severe asthma and negative skin-prick test results. *Chest* 2011; 139(1):190–193.
18. Menzella F, Piro R, Facciolo N, Castagnetti C, Simonazzi A, Zucchi L. Long-term benefits of omalizumab in a patient with severe non-allergic asthma. *Allergy Asthma Clin Immunol* 2011; 7(1):9.
19. Sugino Y, Sanda R, Takagi Y, Kato M, Ohta A, Okumura J, Nagai H. A case of severe asthma responsive to omalizumab treatment despite a low serum IgE level and lack of sensitized allergens. *Arerugi* 2010; 59(11):1572–9.
20. Humbert M, Durham SR, Ying S, Kimmit P, Barkans J, Assoufi B, Pfister R, Menz G, Robinson DS, Kay AB, Corrigan CJ. IL-4 and IL-5 mRNA and protein in bronchial biopsies from patients with atopic and non-atopic asthma: evidence against “intrinsic” asthma being a distinct immunopathologic entity. *Am J Respir Crit Care Med* 1996; 154:1497–04.15.
21. Humbert M, Durham SR, Kimmit P, Powell N, Assoufi B, Pfister R, Menz G, Kay AB, Corrigan CJ. Elevated expression of messenger ribonucleic acid encoding IL-13 in the bronchial mucosa of atopic and non-atopic subjects with asthma. *J Allergy Clin Immunol* 1997; 99:657–65.
22. Ying S, Humbert M, Meng Q, Pfister R, Menz G, Gould HJ, Kay AB, Durham SR. Local expression of e germline gene transcripts and RNA for the e heavy chain of IgE in the bronchial mucosa in atopic and non-atopic asthma. *J Allergy Clin Immunol* 2001; 107:686–92.
23. Humbert M, Grant JA, Taborda-Barata L, Durham SR, Pfister R, Menz G, Barkans J, Ying S, Kay AB. High-affinity IgE receptor (FcεRI)-bearing cells in bronchial biopsies from atopic and non-atopic asthma. *Am J Respir Crit Care Med* 1996; 153:1931–7.
24. Takhar P, Corrigan CJ, Smurthwaite L, O'Connor BJ, Durham SR, Lee TH, Gould HJ. Class switch recombination to IgE in the bronchial mucosa of atopic and non-atopic patients with asthma. *J Allergy Clin Immunol* 2007; 119(1):213–218.
25. Bhat KD, Calhoun WJ. Omalizumab in asthma: is the therapeutic window too small?. *Chest* 2011; 139(1):8–10.
26. Pearlman AN, Chandra RK, Chang D, Conley DB, Tripathi-Peters A, Grammer LC, Schleimer RT, Kern RC. Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. *Am J Rhinol Allergy* 2009; 23:145–148.
27. Bachert C, Claes SE, Tomassen P, van Zele T, Zhang N. Rhinosinusitis and asthma: a link for asthma severity. *Curr Allergy Asthma Rep* 2010; 10:194–201.
28. Mascia K, Haselkorn T, Deniz YM, Miller DP, Bleecker ER, Borish L. TENOR Study Group. Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2005; 116:970–975.
29. Wechsler ME, Kelley JM, Boyd IO, Dutille S, Marigowda G, Kirsch I, Israel E, Kaptchuk TJ. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N Engl J Med*. 2011; 365(2):119–26.
30. Bardelas J, Figliomeni M, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma* 2012; 49(2):144–52.
31. Barbee R, Lebowitz M, Thompson H, Burrows B. Immediate skin-test reactivity in a general population sample. *Ann Intern Med* 1976; 84:129–133.
32. Tschoep JM, Sistek D, Schindler C, Leuenberger P, Perruchoud AP, Wuthrich B, Brutsche M, Zellweger JP, Karrer W, Brandli O. Current allergic asthma and rhinitis: diagnostic efficiency of three commonly used atopic markers (IgE, skin prick tests, and Phadiatop). Results from 8329 randomized adults from the Sapaldia Study. Swiss study on air pollution and lung diseases in adults. *Allergy* 1998; 53:608–613.

APPENDIX

Spanish Registry, Other Authors

1. C Martínez, MD, PhD. Hospital Universitari Germans Trias i Pujol. Universitat Autònoma de Barcelona.
2. Mariana Muñoz MD. Hospital de Bellvitge. C/Feixa Llarga, S/N, 08,907 L'Hospitalet de Llobregat
3. Carlos Almonacid MD. Hospital de Guadalajara. Donantes de Sangre s/n. 19,002 Guadalajara
4. José A Carretero MD, PhD. Hospital Universitario M. Servet. Zaragoza. Isabel La Católica 1–3. 50,009 Zaragoza
5. Elisabet Vera MD—Hospital Universitario M. Servet. Zaragoza. Isabel La Católica 1–3. 50,009 Zaragoza
6. Rosa Irigaray MD. Hospital de Manacor. Ctra. Manacor- Alcúdia, km. 1 07,500 Manacor. Islas Baleares
7. Alejandra Marin MD. Hospital Dos de Maig. Carrer dos de maig, 301. 08,025 Barcelona
8. Benedicta Abejón MD, PhD. Hospital de Terrassa. Ct. Torrebónica, s/n. 08,227 Barcelona
9. Santiago Bardagí MD. Hospital General de Mataró. CTRA. CIRERA, S/N. 608304 Mataró
10. Pilar Ausin MD. Hospital del Mar-IMIM. Passeig Marítim 25–29. 08,003 Barcelona. Centro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias (CIBERES). Ctra. de Sòller Km. 12. 07,110. Bunyola. Palma de Mallorca. Illes Balears.
11. Carles Sanjuas MD, PhD. Hospital del Mar-IMIM. Passeig Marítim 25–29. 08,003 Barcelona. Centro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias (CIBERES). Ctra. de Sòller Km. 12. 07,110. Bunyola. Palma de Mallorca. Illes Balears.
12. Luis M Entrenas MD, PhD. Hospital Universitario Reina Sofía. Córdoba.
13. Alicia Padilla MD. Hospital Costa del Sol. Carretera Nacional 340, km 187, Marbella.
14. Nuria Celorrio MD. Hospital de Viladecans. Av.Gavà, 38. 08,840 Viladecans
15. Marina Blanco-Aparicio MD, PhD. Complejo Universitario A Coruña. Xubias de Arriba, 84 15,006 A Coruña
16. Frederic Tatay MD. Hospital Comarcal de Vinarós. A. Gil De Atrocillo, S/N, 12,500 Vinarós
17. Concepción Cañete MD, PhD. Hospital General de l'Hospitalet de Llobregat. Avinguda Josep Molins, 29–41, 08,906 L'Hospitalet de Llobregat
18. José I Larco MD. Hospital Universitario de La Paz. Pº de la Castellana, 261 28,046 Madrid
19. Teresa Bazús MD. INS-Hospital Universitario Central Asturias. C/Celestino Villamil s/n. 33,006 Oviedo
20. Xavier Muñoz MD, PhD. Hospital Vall d'Hebron. Passeig Vall d'Hebron, 119–129. 08,035 Barcelona
21. María T Sobrevía MD. Hospital Santa María. Av. de l'Alcalde Rovira Roure, 44. 25,198 Lérida
22. Silvia Pascual MD. Hospital de Galdakao. Barrio Labeaga, s/n., 48,960, Galdakao, Vizcaya
23. Isabel Urrutia MD, PhD. Hospital de Galdakao. Barrio Labeaga, s/n., 48,960, Galdakao, Vizcaya
24. José Serrano MD, PhD. Hospital Comarcal de Inca. Carretera Inca-Ilubi, S/N 07,300 Inca. Mallorca. Illes Balears.