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ORIGINAL ARTICLE

Real life study of three years omalizumab in patients with difficult-to-control asthma

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Abstract
Background: Even though there are multiple options for the treatment of asthma, there still exists a fair group of patients with difficult-to-control asthma. We describe for the first time the real-world effects of three-year omalizumab treatment on patients with difficult-to-control asthma, seen in a social security hospital in a Latin American country.
Methods: Difficult-to-control asthmatic patients from the out-patient clinic of a regional hospital were recruited to receive a three-year omalizumab course. Efficacy parameters were asthma control test (ACT) score; FEV1; daily beclomethasone maintenance dose; and unplanned visits for asthma exacerbations (emergency room (ER), hospitalisations, intensive care).
Results: 52 patients were recruited, 47 completed the three-year treatment (42 female, 15–67 years, mean age 43.5). Comparing efficacy parameters of the year before omalizumab with the 3rd year of omalizumab: mean ACT improved from 12.4 to 20.5, mean FEV1 from 66.3% (standard deviation (SD) 19.1%) to 88.4% (SD 16.2%) of predicted, while mean beclomethasone dose reduced from 1750 to 766 mcg/day and there was a significant reduction in patients experiencing ER visits (from 95% to 19%, $p < 0.0001$), hospitalisation (38% to 2%, $p < 0.0001$) and intensive care (4% to 0, NS). Five patients discontinued omalizumab, two because of an adverse event (anaphylaxis, severe headache, both resolved without sequelae).
Conclusion: Omalizumab improved most clinical parameters of Mexican patients with difficult-to-control asthma. Especially the rates of ER visits and hospitalisation were significantly reduced, thus reducing costs. Omalizumab was generally well tolerated.

Introduction

The diagnosis of difficult-to-control asthma is considered in those patients in whom asthma is not well controlled in spite of an adequate therapeutic strategy applied by

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a specialist for the duration of at least six months.[1] This variety and severity of asthma is complex in nature, due to the multiple phenotypes and endotypes that might lead to the persistence of the asthma symptoms, the poor response of the patient to conventional pharmacotherapy, the non-satisfactory evolution of the disease and the susceptibility of the patient to co-morbidities.[2] Apart from the patients with true difficult-to-control asthma there is a considerable group of patients with seemingly difficult-to-control asthma in which the uncontrolled state of their disease is due to other factors, generally poor compliance.

Approximately 5% of all asthmatic patients develop difficult-to-control asthma, resulting in an elevated rate of complications, emergency visits, hospitalisations and even admissions to the ICU.[3] That is why almost half of the total annual cost of asthma treatment corresponds to the severe asthmatic patients.[4] It is important to make an effort to determine the cause of the absence of asthma control. Predisposing factors include an adverse environment, poor compliance, inadequate dosing or a level of asthma maintenance treatment unbalanced in relation to the degree of asthma severity.

Of equal importance is the detection of co-morbidities, e.g. gastro-oesophageal reflux-disease, or the differential diagnosis with other pulmonary disorders, such as chronic obstructive pulmonary disease (COPD), allergic bronchopulmonary aspergillosis, pleuropulmonar eosinophilic syndromes, Churg Strauss syndrome and occupational asthma, among others.[5–7] Several treatment options have been explored to gain control in severe asthmatic patients. Inhaled and systemic corticosteroids have been the cornerstone of most treatment variants and in some cases clinically satisfactory results have been obtained as for the symptomatic and spirometric control of asthma, but the side-effects of long-term high-dose corticosteroid treatment are well-known to the medical community and close monitoring of these patients is mandatory. A small proportion of difficult-to-control asthmatic patients develop corticosteroid resistance, defined as a less than 15% improvement of the forced expiratory volume in the first second (FEV_1) after a 14-day course of 40 mg prednisolone. Asthma control is generally limited in these patients.[5–7]

Omalizumab is a humanised monoclonal antibody that binds to the constant region (Fc) of immunoglobulin E (IgE). Omalizumab blocks the binding of IgE to its high-affinity receptor FcεR1, situated on the surface of the mast cells (and other cells). Consequently, activation of the mast cells and liberation of its pro-inflammatory mediators is inhibited. The efficacy and safety of omalizumab in patients – six years and above – with severe asthma and difficult-to-control asthma have been documented in multiple clinical trials.[8] As a consequence, omalizumab has been integrated in major clinical guidelines on the treatment of asthma, as a treatment option in the last step of therapy, in those patients not well controlled on high dose inhaled corticosteroids in combination with long-acting beta-agonists.[5,9–11] Therefore, the objective of this study is to describe the results obtained after three years of treatment with omalizumab in patients with moderate to severe difficult-to-control asthma in a tertiary hospital in Mexico City.

Materials and methods

We conducted an open prospective, observational, cohort study, describing the evolution of difficult-to-control moderate to severe asthmatic patients, recruited from the out-patients clinic of the Allergy and Immunology Department of the Regional Hospital *Licenciado Adolfo López Mateos* (ISSSTE), in Mexico City. Patients fulfilling the inclusion criteria were invited to a thirty-six months' course of omalizumab. The study was implemented from January 2009 through December 2012. Patients from 12 to 75 years of age, of either sex, fulfilling the American Thoracic Society (ATS) criteria for difficult-to-control asthma[6] were invited to participate and recruited into the study once an informed consent form had been signed. The following were exclusion criteria: COPD, occupational asthma, cystic fibrosis, cardiac insufficiency grade 3 or higher according to the New York Heart Association classification,[12] severe pulmonary emphysema, disorders that cause laryngeal or trachea obstruction, carcinoid syndromes, hyperthydoidism, sleep apnoea and psychiatric disorders. An unacceptable dosing interval between two doses of omalizumab or a no-show of the patient for the next injection were elimination criteria.

Omalizumab (XOLAIR®) was administered subcutaneously to all patients. The omalizumab dose was calculated according to the guidelines of the manufacturer, taking into account total IgE serum levels and the patient's weight.

Depending on the administration schedule of omalizumab the patients were evaluated every 15 days or every month during the three-year surveillance. The Asthma Control Test™ (ACT) was taken at the beginning and at the end of the study.[13] The ACT™ is a simple five-point questionnaire, which is self-completed by patients. Each item is scored from one (poor control) to five (good control), related to the frequency and severity of the symptoms and their impact on the patient's quality of life; the scores of each of each of the five questions are added up to give a final score with a maximum of 25. The total score of the ACT™ should be interpreted in the following way: 14 or less is considered as very poor control of asthma, 15–19 total score is un-controlled asthma, 20–24 total score reflects well controlled asthma and finally 25 points is completely controlled asthma. We compared initial ACT™ values of our patients with ACT™ scores at the end of three years of omalizumab administration to evaluate the impact of the monoclonal antibody on asthma control. Moreover, pulmonary function tests were carried out (World Spirometer Easyone 2001) and pre-bronchodilator FEV_1 was recorded in percent of the predicted value, according to anthropometric characteristics, sex, race and a history of tobacco smoke exposure.

Before the study started and during the surveillance period unscheduled visits to the clinic because of asthma exacerbations were recorded. These unscheduled visits were classified according to their nature (emergency department, hospitalisation, intensive care unit (ICU)) and expressed as unscheduled visits per year. Additionally, the start dose and the final dose of beclomethasone were documented, as well as the intake of any systemic glucocorticosteroids. No detailed record was kept on other asthma medication taken, so only a general picture can be given on this issue. A log of adverse events possibly or