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Asthma control in severe asthmatics under treatment with omalizumab: A cross-sectional observational study in Italy

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ABSTRACT

Few data are available on the proportion of asthmatics achieving a good asthma control (according GINA guidelines) and on the level of airway inflammation during omalizumab treatment.

The aim of this cross-sectional national observational study was to assess the level of control (according to GINA guidelines) achieved in a group of asthmatics on omalizumab treatment, and to characterize the factors that influence the lack of control.

We studied 306 asthmatics under omalizumab treatment for a median of 32 months (range 4–120). The level of control according to GINA was good in 25.2%, partial in 47.1% and poor in 24.5% of patients (data were missing for the remaining 3.2%). Comparison between poorly controlled and partially or well controlled asthmatics showed a statistically significant higher prevalence of some comorbidities in the first group, namely obesity, gastro-oesophageal reflux disease (GORD), aspirin intolerance and mental disorders (all $p < 0.001$). Similarly, asthmatics with at least one exacerbation in the last year showed a significantly higher prevalence of obesity, chronic rhinosinusitis, nasal polyps, GORD, and aspirin intolerance (all $p < 0.05$) than patients without exacerbations. When we selected patients without relevant comorbidities (upper airways disease, GORD, obesity, aspirin intolerance) and not currently

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smoking ($N = 73$), the percentage of well or partially controlled asthmatics was significantly higher than in patients with comorbidities (84.9% vs 71.1%, $p = 0.02$); the rate of asthmatics without exacerbations in the last year was also higher (73.6% vs 51.1%, $p = 0.001$).

During omalizumab treatment, a high percentage of asthmatics obtain a good or partial control of asthma. Comorbidities are associated with the lack of asthma control and persistence of exacerbations.

1. Introduction

Patients with severe asthma represent one of the major problems in the management of this disease. Although severe asthmatics account for only 5%–10% of asthma population, they are responsible for more than 80% of the total health cost for asthma [1]. These patients are usually treated with high-dose inhaled corticosteroids (ICS) plus long-acting-beta2agonist (LABA), often associated with other drugs (montelukast, theophylline, tiotropium), but despite a high burden of pharmacologic treatment the control of the disease is only occasionally obtained and the patients continue to experience diurnal and nocturnal symptoms, frequent exacerbations requiring oral steroids and/or hospitalization, and poor quality of life with substantial limitations in daily life activity [2].

In recent years, omalizumab (Xolair), a monoclonal antibody directed vs human IgE, has been introduced for the treatment of severe allergic asthma. The hypothesis was that minimizing free serum IgE concentration and then binding to IgE receptor-bearing inflammatory cells, the whole allergic cascade would be blocked at the beginning, thus leading to improvement of the airway inflammatory pattern and potentially to the airway remodeling [3]. In this very selected target population the high cost of the treatment is balanced by a high efficiency in patients with a high asthma-related burden, leading then to a favorable cost-effectiveness ratio [4]. Registrative and post-registrative studies have largely demonstrated that omalizumab induced a great reduction in asthma exacerbations (particularly those associated to emergency department access or hospitalization) and a substantial improvement in quality of life [5–7].

After the entry on the market, several observational studies have been published, showing the high efficacy of omalizumab in real life. After the first observations performed in France, Germany and Belgium [8–10], many other regional studies have been performed, with the aim of describing the outcome of asthma in samples of severe asthmatics treated with omalizumab: while the majority of these studies included relatively small groups of patients followed for few months or years, only few national or international registries have evaluated the outcome of asthma after long-term treatment with omalizumab (e.g. up to 6 years) in hundreds of patients, confirming in the real life the high efficacy of omalizumab in terms of reduction of symptoms, exacerbations, pharmacologic burden, and improvement in quality of life in adults [11–17] and in children [18]. However, none of these studies have evaluated the real asthma control level according to GINA, or some markers of airway inflammation, such as sputum or blood eosinophils or exhaled nitric oxide (eNO).

In Italy, omalizumab has been available since 2007, and its use is limited to patients with severe uncontrolled asthma associated with allergic sensitization to perennial allergens and a well defined ratio between serum IgE and body weight. A first multicenter observational study analyzed the data of the first group of Italian patients ($N = 142$) treated from at least 4 months and up to 12 months with omalizumab [19]. Data were limited to the informations included in the AIFA register (number of exacerbations, concomitant medication, global assessment of efficacy). The results of this study confirmed the very low number of exacerbations during omalizumab treatment and the high level of efficacy obtained in almost all the examined patients.

Some years after this the first observation, Italian researchers aimed to verify the current level of real asthma control in a large, unselected sample of severe allergic asthmatics treated for several years with omalizumab, with the attempt to include some more standardized measurements of the level of asthma control, pulmonary function measurements and biomarkers of airway inflammation. In particular, we would like to assess the percentage of these patients who gained a well or a partial control of asthma during omalizumab treatment, and if this was associate with specific characteristics of the patients.

2. Patients and methods

This cross-sectional observational study was performed in 26 italian centers (the list of the contributors is reported in the Appendix). All patients attending the centers for the regular administration of omalizumab were asked to participate to the study. The study protocol was approved by the Ethic Commitee of the Coordinator Centre (Ethic Commettee of the University Hospital of Pisa, protocol FPR0001 no. 3436, approved 10 nov 2011) and later on by all Ethic Committees of the different Italian centers. Informed consent was obtained from all participants.

Patients underwent a detailed questionnaire in order to analyze the characteristics of asthma at the time of the observation. Several sections were considered: a) anthropometric data, including age, gender, body mass index (BMI), education level and area of residence; b) clinical history of asthma: age of onset, skin sensitivity, serum IgE levels, methods of diagnosis; c) current level of asthma treatment (with great detail on the dose of the different ICS and on whether all treatments were left unmodified, increased or reduced after the beginning of omalizumab treatment), duration of the omalizumab treatment, adherence to the treatment, and assessment of the correct use of the inhalers; potential local or systemic side effects of omalizumab treatment were also investigated; d) number and severity of comorbidities (allergic rhinitis, rhinosinusitis, nasal polyps, gastro-oesophageal reflux disease (GORD), aspirin intolerance, psychiatric disorders, obstructive sleep apnea, etc), with the evaluation whether during omalizumab treatment these comorbidities improved or not; e) exposure to pollutants or irritants, including smoking habit; f) number and characteristics of exacerbations, both during the whole period of omalizumab treatment and in the last year; number of unscheduled visits to GPs and pulmonary specialists, number of hospitalizations or emergency room accesses, both before and after omalizumab treatment, number of days of oral corticosteroids use, number of days of work or school lost owing to the disease. **All these informations were collected by the record forms of each patient, where they were reported both in the pre- and in the post-omalizumab treatment period. As regards comorbidities, only those which had a documented demonstration (e.g. report of an ENT evaluation or CT scan of**

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