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Response to omalizumab in patients with severe allergic asthma: A real-life study

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ABSTRACT

Introduction: Omalizumab is a humanized monoclonal anti-IgE antibody, which is widely used for patients with severe uncontrolled asthma. Treatment with omalizumab is known to decrease the number of exacerbations and GETE score (Global Evaluation of Treatment Effectiveness) - but little is known about which patients benefit the most. Moreover, the time to discontinuation of the treatment with omalizumab has yet to be investigated. In this real-life study on a Danish population we explore these important issues.

Method: In a retrospective real-life study, 54 patients treated with omalizumab at a specialized outpatient asthma clinic were included. Change in GETE score, time to discontinuation of treatment and associated risk factors were analysed.

Results: As a result of omalizumab treatment, most patients improved in GETE score from poor/worsening to excellent. Women were treated for a median time of 31 months (95% CI: 4.6–57.4) and approximately 50% of patients discontinued treatment after 500 days whilst, for men, 50% discontinued treatment after 1500 days. Eosinophil count above 300 cells/μL at treatment initiation was positively related to the discontinuation of omalizumab (HR 4.3 95%CI (1.22–15.28) p = 0.023).

Conclusion: In conclusion, female gender and an eosinophil count above 300 cells/μL may predict a better treatment response, leading to a shorter treatment time than the current guideline recommendation of maximum 48 months. Additionally, the GETE score improves with omalizumab. More real-life studies are needed to determine which patients will benefit the most from the treatment.

1. Introduction

As many as 300 million people worldwide [1] and 300,000 [2] adults in Denmark have asthma. Approximately 10% of all asthma patients suffer from severe asthma. It is suggested that severe asthma is not just more asthma symptoms but rather should be considered a different type of asthma [3].

Asthma is characterized by reversible obstruction, hyperresponsiveness and local inflammation of the airways. Moreover, release of inflammatory markers leads to remodeling of the airway mucosa, increased mucus secretion, proliferation of smooth muscle cells, and fibrosis. Asthma is associated with sensitivity to environmental challenges such as allergens and production of IgE [4,5].

According to the GINA guidelines [1] asthma is treated with a combination of inhaled corticosteroids (ICS) and beta-agonists (SABA/LABA). GINA divides asthma patients into [5] steps according to severity. In the most severe treatment step a combination of ICS/LABA and SABA is recommended with omalizumab as add-on therapy. 55% of this group of patients often experience lack of asthma control, frequent exacerbations [6] and reduced quality of life because of asthma [7].

Omalizumab is a humanized monoclonal anti-IgE antibody. It is injected subcutaneously either monthly or bi-monthly in addition to preexisting asthma medication. Omalizumab neutralizes the large amounts of circulating free IgE produced under allergic

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asthma responses. Hereby less IgE is available to induce an allergic response when an allergen is encountered.

Omalizumab is used in patients with severe uncontrolled allergic asthma with a positive skin prick test to a perennial aeroallergen, low lung function (FEV1<80%), daily symptoms and frequent exacerbations in spite of the use of relevant asthma medication. The effect of omalizumab is evaluated after 16 weeks of treatment. The treatment is continued if a positive effect on the severity of asthma symptoms is seen.[8].

The effect of omalizumab has been evaluated in several clinical trials and real life studies. Real-life studies have shown a positive effect of omalizumab on many parameters; reduction in the number of exacerbations, fewer daily and nightly symptoms, better asthma control according to ACQ (asthma control questionnaire), improvement in asthma related quality of life, lower GETE (global evaluation of treatment effectiveness), fewer hospitalizations and less usage of ICS.[9].

The aim of this study was to evaluate the effectiveness and safety as well as predictors of drug survival of omalizumab, and to estimate the change in GETE according to different disease characteristics in patients with severe allergic asthma treated with omalizumab.

2. Methods

2.1. Patients

In a specialized outpatient asthma clinic at the Department of Respiratory Medicine, Bispebjerg Hospital, Copenhagen, Denmark, consecutive patients (n = 54) treated with omalizumab between 2009 and 2015 were included. All patients had severe asthma; of the entire group, two had no history of allergic perennial asthma. Specific allergen status was unobtainable in three patients in this retrospective study, but admission to treatment was given on the grounds of perennial allergy.

All patients received omalizumab as add-on therapy [10] in accord with national Danish guidelines: Patients >6 years of age with severe allergic asthma, treated with high doses of ICS/LABA, a positive skin prick test for perennial allergens, and more than 2 exacerbations in the past 6 months, with an impaired lung function (FEV1 < 80% of predicted value) and an IgE level within the recommendation for omalizumab treatment.[11].

After initiation of omalizumab the treatment effectiveness, safety and concomitant medication was monitored by the treating pulmonologist.

Inclusion criteria: All patients aged 18 years or more who received treatment with omalizumab.

Exclusion criteria: Patients meeting the criteria for omalizumab treatment but never receiving the treatment.

2.2. Study design

In this real life study, data from the patient records were retrospectively collected. The Danish Health Authority approved the collection of data (Journal. N. 3-3013-1454/1).

For each patient we noted: lung function, serum total IgE-level, omalizumab dose and duration, type of allergy, value of exhaled nitric oxide (NO), blood eosinophil-count, gender, age, symptoms when initiating treatment, and symptoms when treatment was terminated according to the GETE equivalent.

The GETE score evaluates multiple aspects to determine the response to omalizumab treatment based on patient interviews, severity of symptoms, usage of medication and spirometry examinations [12]. The GETE score is a five-point scale dividing the patients according to the asthma symptoms into; excellent, good, moderate, poor or worsening of symptoms. A responder is defined as a patient with good/excellent symptom score when treated with omalizumab.[13].

After four months of treatment the effect was evaluated by the treating pulmonologist. If the patient experienced improvement in asthma symptoms and/or no exacerbations, the patient continued the treatment with an evaluation on regular consultations with the pulmonologist.

All the patients were grouped into perennial or perennial plus pollen sensitized as treatment with omalizumab is recommended for patients with perennial allergy independent of pollen allergy [8].

2.3. Medication and dosing

All patients received omalizumab in the dose determined by the omalizumab dosing chart using the baseline IgE (30-1500 IE/ml) and the weight of the patient. Nurses at the asthma clinic administrated the injections of omalizumab monthly or bi-monthly.

2.4. Statistical analysis

The data analysis was performed using SPSS statistical software (SPSS Inc., Chicago, Illinois) version 22. Means were calculated for normally distributed data and medians for skewed distributed data. Median drug survival of omalizumab according to covariates; gender, age group, blood eosinophil count at initiation, serum total IgE at initiation, dose of omalizumab, FeNO at initiation, type of allergy (perennial and perennial plus pollen) and asthma symptoms at initiation (GETE score) was explored by the Kaplan-Meier method. Proportional hazards regression was used to determine the hazard ratio (risk) for omalizumab discontinuation according to the different covariates. P-values <0.05 were considered statistically significant.

3. Results

In total, 54 patients (29 women) were treated with omalizumab at a median dose of 300 mg. The characteristics of the patients are shown in Table 1.

The GETE score was similar among the allergy groups at treatment initiation. The majority (70%) of the patients had experienced poor or worsening of their asthma symptoms and none experienced excellent control. In contrast as many as 59% of these patients experienced excellent asthma control while treated with omalizumab and only 7% poor or worsening of symptoms (Fig. 1).

Table 1
Baseline statistics.

Variable (Range)	Women	Men
N	29 (54%)	25 (46%)
Age	37 (43)	37 (43)
Blood eosinophil count	80 (1020)	290 (930)
IgE before treatment	262 (1976)	263 (2500)
Omalizumab dose, mg	300 (450)	300 (600)
FEV1 at initiation	2.8 (2.4)	2.7 (3.8)
FeNO at initiation	21 (85)	39 (99)
Months of treatment	15 (95)	24 (83)
Treatment time > 4 years	9	7
Allergen positive, no.		
Animal	17	16
Mold	4	3
Dust	12	14
Pollen	26	23

1. No of missing values: Eosinophil count; 14, IgE: 9, FeNO: 23, FEV1:22.
2. All values are in median.