



# 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/ $\mu$ L 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/ $\mu$ L 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.

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## 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, hyper-responsiveness 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 aero-allergen, 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 administered 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.

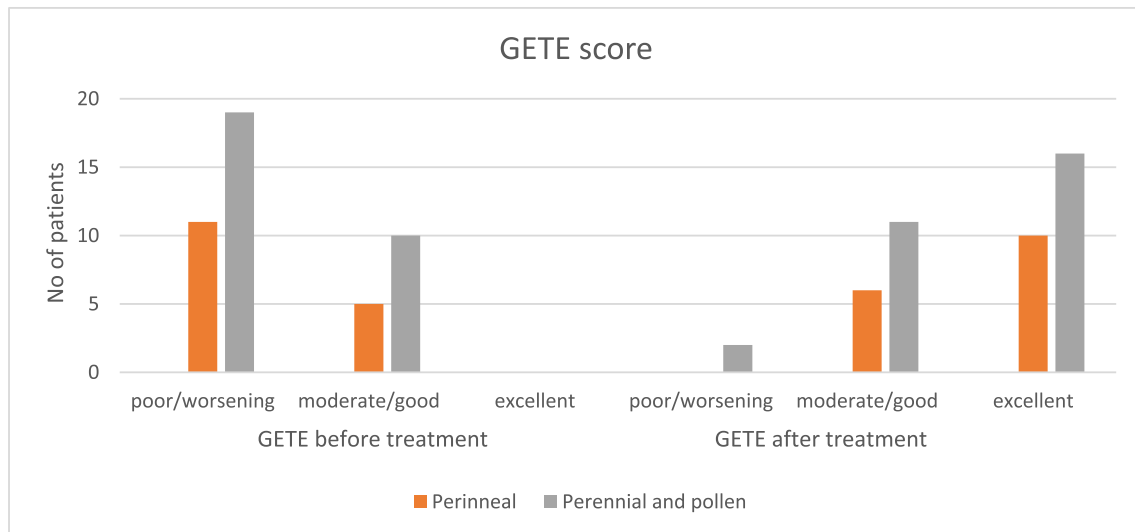


**Fig. 1.** Omalizumab effectiveness as evaluated with the GETE Questionnaire.

The median duration of omalizumab treatment summed over all patients was 31 months (95% CI 4.6–57.4) (Fig. 2). None of the explored covariates: gender, age, serum total IgE at initiation, omalizumab dose, FeNO at initiation, GETE at initiation or type of allergic sensitization were statistically significantly related to the risk of omalizumab discontinuation. After multiple adjustment a blood eosinophil count at initiation (above 300 cells  $\mu\text{L}$ ) showed

to be significantly positively related to discontinuation of omalizumab treatment with a HR = 4.3 and a 95%CI (1.22–15.28),  $p = 0.023$  (Table 2).

Three patients experienced side effects; two had injection-site reactions (one led to treatment discontinuation) and one experienced fever after omalizumab injection.

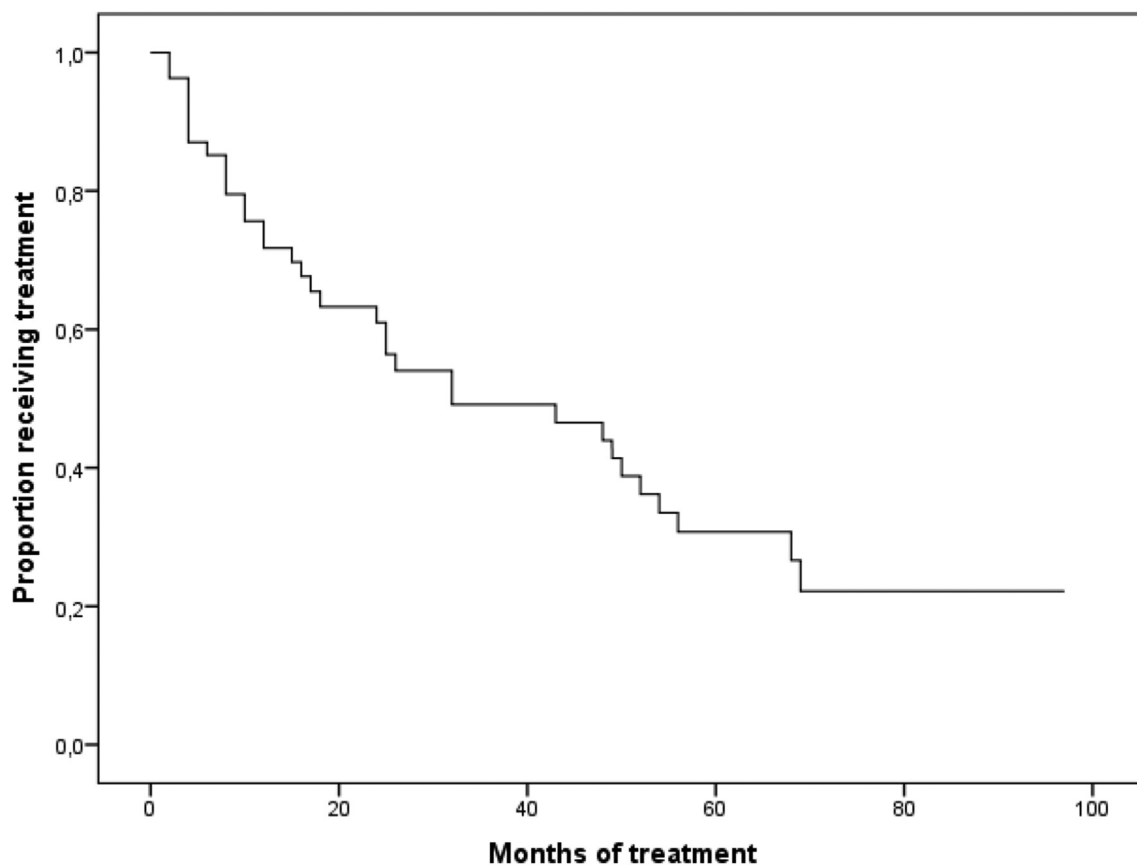


**Fig. 2.** Drug survival of omalizumab.

**Table 2**

Time to discontinuation of omalizumab treatment according to patient characteristics.

| Variable               | Time to Discontinuation (median, 95% CI) | Hazard ratio (95% CI) | P-value | Adjusted Hazard ratio (95% CI) | P-value      |
|------------------------|------------------------------------------|-----------------------|---------|--------------------------------|--------------|
| Gender                 |                                          |                       |         |                                |              |
| Women                  | 523 (129–917)                            | 1.00                  | 0.405   | 1.00                           |              |
| Men                    | 1434 (548–2320)                          | 0.75 (0.38–1.49)      |         | 0.79 (0.28–2.20)               | 0.661        |
| Age                    |                                          |                       |         |                                |              |
| ≤39                    | 1771 (1361–2181)                         | 1.00                  |         | 1.00                           |              |
| ≥40                    | 2645 (1503–3787)                         | 1.12 (0.57–2.18)      | 0.750   | 1.2 (0.28–4.76)                | 0.835        |
| Blood eosinophil count |                                          |                       |         |                                |              |
| <299                   | 1470 (722–2218)                          | 1.00                  |         | 1.00                           |              |
| ≥300                   | 739 (182–1296)                           | 1.53 (0.68–3.44)      | 0.307   | 4.3 (1.22–15.28)               | <b>0.023</b> |
| IgE at initiation      |                                          |                       |         |                                |              |
| ≤99 KU/L               | 1306 (641–1971)                          | 1.00                  |         | 1.00                           |              |
| ≥100 KU/L              | 770 (0–1587)                             | 1.11 (0.47–2.61)      | 0.811   | 0.77 (0.12–4.94)               | 0.783        |
| Omalizumab dose        |                                          |                       |         |                                |              |
| ≤299 mg                | 1434 (1111–1756)                         | 1.00                  |         |                                |              |
| ≥300 mg                | 953 (674–1232)                           | 1.13 (0.54–2.38)      | 0.744   |                                |              |
| FeNO at initiation     |                                          |                       |         |                                |              |
| ≤20 (ppb)              | 738 (345–1131)                           | 1.00                  |         |                                |              |
| ≥21 (ppb)              | 510 (72–948)                             | 0.83 (0.34–2.04)      | 0.681   |                                |              |
| GETE at initiation     |                                          |                       |         |                                |              |
| Poor/worsening         | 1434 (767–2101)                          | 0.56 (0.28–1.19)      | 0.136   | 0.29 (0.074–1.18)              | 0.086        |
| Moderate/good          | 728 (228–1228)                           | 1.00                  |         | 1.00                           |              |
| Allergy                |                                          |                       |         |                                |              |
| Perennial              | 1554 (51–3057)                           | 1.00                  |         | 1.00                           |              |
| Perennial and Pollen   | 1306 (371–2241)                          | 1.60 (0.69–4.07)      | 0.254   | 1.1 (0.27–4.75)                | 0.852        |

P &lt; 0.05 were considered statistically significant.

## 4. Discussion

### 4.1. Effect of treatment

The majority of patients with a severe GETE score at initiation experience a shift in GETE from poor/worsening to excellent asthma control, which underlines the effectiveness of the treatment in terms of asthma control and overall symptom severity as seen in other studies [14]. Our data indicated that patients with a poor/worsening GETE score at initiation tend to receive treatment for a longer period of time. This could be due to more uncontrolled asthma.

We speculate that the administration of treatment is a part of the success because of the high degree of compliance to omalizumab. If the same degree of compliance was observed for the concomitant inhalant asthma medication this might lead to the same reduction in exacerbations and better asthma control [15].

Earlier studies have proven omalizumab to have a great safety profile [16]. This is confirmed in this study with only three cases of side effects. Only one patient ended the treatment due to side effects.

### 4.2. Evaluation of treatment duration

In total, 16 patients (30%) had been treated for more than the recommended four years due to recurrent exacerbations after ended treatment. This demonstrates how some patients may need omalizumab for a longer period of time – maybe lifelong – while others can end their treatment after four years as current guidelines suggest. The patients in this study with the longest duration of treatment had been treated for eight years and are still receiving treatment with omalizumab.

Our study is the first to report the drug survival of omalizumab in a long-term real life study. The survival function of the proportion of patients receiving omalizumab demonstrates how the fraction of women still treated with omalizumab declines faster than men. Approximately 50% of the women had ended treatment

after 500 days. In contrast 50% of the men were still treated after 1500 days. Thus, it seems like the effect is seen earlier among women than among men. For both groups 20% of the patients continue treatment for as long as 3000 days.

Moreover, the male patients had a higher eosinophil count and IgE than females suggesting more severe and less controlled asthma among men [17]. An eosinophil count of min. 150 cells pr.  $\mu$ L has been shown to be a cut-off value for the optimal effect of omalizumab, measured as a reduction of exacerbations.[18] This correlates well with the baseline eosinophil count of 290 cells per  $\mu$ L observed in the men included in this study. In contrast, the baseline eosinophil count for women was only 80 cells pr.  $\mu$ L, this could indicate a possible lower threshold than the 150 cells pr.  $\mu$ L, as the women ended treatment after a shorter period of time.

Our study showed how patients with a high blood eosinophil count above 300 cells pr.  $\mu$ L, on average are treated for a shorter period than patients with a low eosinophil count. This highlight the role of eosinophilic inflammation in allergic [19] asthma and the need of further research in this area to determine if the eosinophil count should be evaluated in relation to omalizumab treatment.

## 5. Conclusion

In conclusion, female gender and an eosinophil count above 300 cells/ $\mu$ L may predict a better treatment response to omalizumab, 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.

## Conflict of interests

Simon Francis Thomsen is an advisory board member and speaker for Novartis.

Vibeke Backer is an advisory board member and speaker for Novartis.

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## References

- [1] <http://ginasthma.org/> Date: 09.05.2017.
- [2] <https://www.lunge.dk/astma>. Date: 09.05.2017.
- [3] The ENFUMOSA, cross-sectional European multicenter study of the clinical phenotype of chronic severe asthma. *European Network for Understanding Mechanisms of Severe Asthma*, *Eur. Respir. J.* 22 (2003) 470–477.
- [4] S.T. Holgate, Innate and adaptive immune responses in asthma, *Nat. Med.* 18 (2012) 673–683, <http://dx.doi.org/10.1038/nm.2731>.
- [5] W.D. Arroyave, F.A. Rabito, J.C. Carlson, The relationship between a specific IgE level and asthma outcomes: results from the 2005–2006 National Health and Nutrition Examination Survey, *J. Allergy Clin. Immunol. Pract.* 1 (2013) 501–508, <http://dx.doi.org/10.1016/j.jaip.2013.06.013>.
- [6] J.L.R. Hermosa, C.B. Sánchez, M.C. Rubio, M.M. Mínguez, J.L.A.-S. Walther, Factors associated with the control of severe asthma, *J. Asthma* 47 (2010) 124–130, <http://dx.doi.org/10.3109/02770900903518835>.
- [7] B.E. Chipps, R.S. Zeiger, L. Borish, S.E. Wenzel, A. Yegin, M.L. Hayden, D.P. Miller, E.R. Bleecker, F.E.R. Simons, S.J. Szefer, S.T. Weiss, T. Haselkorn, TENOR Study Group, Key findings and clinical implications from the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study, *J. Allergy Clin. Immunol.* 130 (2012) 332–342, <http://dx.doi.org/10.1016/j.jaci.2012.04.014> e10.
- [8] Xolair, Ficha Técnica del medicamento. The European Agency for the Evaluation of Medicinal Products (EMA). Committee for Proprietary Medicinal Products (CPMP). European Public Assessment Report (EPAR): Xolair, Available from: <http://www.ema.europa.eu>. Date 03.03.2017.
- [9] I. Abraham, A. Alhossan, C.S. Lee, H. Kutbi, K. MacDonald, “Real-life” effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review, *Allergy* 71 (2016) 593–610, <http://dx.doi.org/10.1111/all.12815>.
- [10] <http://www.lungemedicin.dk/fagligt/66-omalizumab.html#varidhed>[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000606/human\\_med\\_001162.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000606/human_med_001162.jsp&mid=WC0b01ac058001d124). Date 09.05.2017.
- [11] <http://www.lungemedicin.dk/fagligt/66-omalizumab.html#varidhed>. Date 09.05.2017.
- [12] J. Bousquet, Z. Siergiejko, E. Swiebocka, M. Humbert, K.F. Rabe, N. Smith, J. Leo, C. Peckitt, R. Maykut, G. Peachey, Persistency of response to omalizumab therapy in severe allergic (IgE-mediated) asthma, *Allergy* 66 (2011) 671–678, <http://dx.doi.org/10.1111/j.1398-9995.2010.02522.x>.
- [13] M. Cazzola, G. Camiciottoli, M. Bonavia, C. Gulotta, A. Ravazzi, A. Alessandrini, M.F. Caiaffa, A. Berra, P. Schino, P.L. Di Napoli, R. Maselli, G. Pelaia, E. Buccchioni, P.L. Paggiaro, L. Macchia, Italian real-life experience of omalizumab, *Respir. Med.* 104 (2010) 1410–1416, <http://dx.doi.org/10.1016/j.rmed.2010.04.013>.
- [14] M. Cazzola, G. Camiciottoli, M. Bonavia, C. Gulotta, A. Ravazzi, A. Alessandrini, M.F. Caiaffa, A. Berra, P. Schino, P.L. Di Napoli, R. Maselli, G. Pelaia, E. Buccchioni, P.L. Paggiaro, L. Macchia, Italian real-life experience of omalizumab, *Respir. Med.* 104 (2010) 1410–1416, <http://dx.doi.org/10.1016/j.rmed.2010.04.013>.
- [15] L. Hendeles, Y.R. Khan, J.J. Shuster, S.E. Chesrown, M. Abu-Hasan, Omalizumab therapy for asthma patients with poor adherence to inhaled corticosteroid therapy, *Ann. Allergy Asthma Immunol.* 114 (2015) 58–62, <http://dx.doi.org/10.1016/j.anai.2014.10.012> e2.
- [16] S.T. Holgate, A.G. Chuchalin, J. Hébert, J. Lötvall, G.B. Persson, K.F. Chung, J. Bousquet, H.A. Kerstjens, H. Fox, J. Thirlwell, G.D. Cioppa, Omalizumab 011 International Study Group, Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma, *Clin. Exp. Allergy* 34 (2004) 632–638, <http://dx.doi.org/10.1111/j.1365-2222.2004.1916.x>.
- [17] T.N. Tran, D.B. Khatry, X. Ke, C.K. Ward, D. Gossage, High blood eosinophil count is associated with more frequent asthma attacks in asthma patients, *Ann. Allergy Asthma Immunol.* 113 (2014) 19–24, <http://dx.doi.org/10.1016/j.anai.2014.04.011>.
- [18] H.G. Ortega, S.W. Yancey, B. Mayer, N.B. Gunsoy, O.N. Keene, E.R. Bleecker, C.E. Brightling, I.D. Pavord, Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies, *Lancet Respir. Med.* (2016), [http://dx.doi.org/10.1016/S2213-2600\(16\)30031-5](http://dx.doi.org/10.1016/S2213-2600(16)30031-5).
- [19] M.E. Rothenberg, Eosinophilia, *N. Engl. J. Med.* 338 (1998) 1592–1600, <http://dx.doi.org/10.1056/NEJM199805283382206>.